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BLOOD COAGULATION IN DISSEMINATED SCLEROSIS AND OTHER DISEASES OF BRAIN STEM AND CORD

BENJAMIN SIMON, M.D.*

MIDDLETOWN, CONN.

In 1935 Simon and Solomon [1] published studies on the coagulation responses of the blood in disseminated sclerosis. Their theoretic considerations sprang from the observations of many workers [2] that exacerbations of symptoms in disseminated sclerosis are often related to trauma, operation, exposure, immersion, pregnancy, infection, emotional excitement, etc.—factors cited by Pickering [3] as predisposing to disturbances in the blood plasma and to thrombosis. The hypothesis that a common denominator in these situations might be a disturbance in the coagulation reactions of the blood offers a clinical basis for the observations of Putnam and associates [4] that the lesions in disseminated sclerosis are the result of venous thromboses in the brain and spinal cord.

* Now serving in the Medical Corps of the United States Army.

This investigation was carried out in the National Hospital, Queen Square, London, during the tenure of a Rockefeller Fellowship in Neurology.

Permission to study patients in their respective services was given by Drs. Denis Brinton, E. Arnold Carmichael, MacDonald Critchley, Gordon Holmes, S. M. Hinds Howell, George Riddoch, Grainger Stewart and F. M. R. Walshe.

1. Simon, B., and Solomon, P.: Multiple Sclerosis: Effect of Typhoid Vaccine and of Epinephrine on Coagulation of the Blood, Arch. Neurol. & Psychiat. **34:** 1286 (Dec.) 1935. Solomon, P., and Simon, B.: The Blood Coagulation in Cases of Multiple Sclerosis, ibid. **33:**1383 (June) 1935.

2. Berger, A.: Eine Statistik über 206 Fälle von multipler Sklerose, Jahrb. f. Psychiat. u. Neurol. **25:**168, 1905. Jelliffe, S. E.: Multiple Sclerosis: Its Occurrence and Etiology, J. Nerv. & Ment. Dis. **31:**446, 1904. Marie, P.: Sclérose en plaques et maladies infectieuses, Progrès méd. **12:**287, 305, 349 and 365, 1884. Oppenheim, H.: Aerztliches Gutachten betreffend die Erkältungs-Aetiologie der multiplen Sklerose, Med. Klin. **7:**1517, 1911. Palmer, W. T.: Case of Disseminated Sclerosis Following Injury, West London M. J. **12:**219, 1907. Woodbury, M. S.: A Probable Etiologic Factor in Multiple Sclerosis, Arch. Neurol. & Psychiat. **1:**408 (April) 1919.

3. Pickering, J. W.: The Blood Plasma in Health and Disease, New York, The Macmillan Company, 1928.

(Footnotes continued on next page)

Simon and Solomon [1a] found that in both control cases and cases of disseminated sclerosis there was a definite drop in coagulation time after the intravenous administration of typhoid vaccine. They observed, also, a similar, but briefer, reaction to the subcutaneous administration of epinephrine. In general, it was found that the shortening of clotting time was greater, although not notably so, in cases of disseminated sclerosis. It was observed, however, that the reduction in clotting time was prolonged approximately three times as long in the cases of disseminated sclerosis as in the control cases. The investigators suggested that this disturbance in blood coagulation might be the mechanism through which intravascular thromboses were produced as a consequence of the stimuli mentioned.

Since the work of Simon and Solomon [1a] additional contributions to the subject have appeared. Putnam and other workers [5] have further shown by experiment and in clinical material the relationship of the plaques to thrombosed venules. In 1937 Putnam [6] summarized his views as follows:

> It seems probable that the primary alteration in certain types of "encephalomyelitis" and multiple sclerosis is an abnormal lability of the blood plasma, which may be caused to clot in venules of the brain (and other organs) by a variety of exogenous (and probably also endogenous) factors.

Later, the same author [7] asserted:

> There is no indication that the primary cause of the thrombosis exists in the wall of the vessel. It appears that it should exist therefore in the circulating blood.

An interesting corroborative observation was made by Alexander and Myerson [8] in their microincineration studies. They found the mineral architecture of plaques to be quite similar to that seen in foci

4. Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: I. The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931. Putnam, T. J.; McKenna, J. B., and Evans, J.: Experimental Multiple Sclerosis in Dogs from Injection of Tetanous Toxin, J. f. Psychol. u. Neurol. **44**:460, 1932. Putnam, T. J.: Pathogenesis of Multiple Sclerosis, New England J. Med. **209**:786 (Sept. 7) 1933; The Biological Significance of the Lesions of Multiple Sclerosis, Science **80**:295 (Sept. 28) 1934; Studies in Multiple Sclerosis: IV. "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction, Arch. Neurol. & Psychiat. **33**:929 (May) 1935.

5. (*a*) Putnam, T. J.: Studies in Multiple Sclerosis: VIII. Etiologic Factors in Multiple Sclerosis, Ann. Int. Med. **9**:854 (Jan.) 1936. (*b*) Putnam, T. J., and Adler, A.: Vascular Architecture of the Lesions of Multiple Sclerosis, Arch. Neurol. & Psychiat. **38**:1 (July) 1937.

6. Putnam, T. J.: Lesions of "Encephalomyelitis" and Multiple Sclerosis, J. A. M. A. **108**:1477 (May 1) 1937.

7. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298 (June) 1937.

8. Alexander, L., and Myerson, A.: The Mineral Content in Cerebral Lesions, J. Nerv. & Ment. Dis. **84**:313 (Sept.) 1936.

of softening, with areas of demineralization about highly mineralized blood vessel areas. In every one of 14 cases of multiple sclerosis, Putnam [5a] observed pronounced vascular changes, with engorgement, tortuosity and proliferation of veins, in the vicinity of plaques. These were not seen in the vicinity of old softenings. This substantiated Putnam's [6] conclusions that the changes were primary, and not secondary.

The question whether the disturbance in blood coagulation precedes or follows the inception of disseminated sclerosis logically requires an answer. From the work of Cannon [9] and that of Simon and Solomon [1a] it could be argued that disseminated sclerosis produced changes in the autonomic nervous system which would cause changes in blood coagulability. This was also suggested by Haug,[10] who observed disordered carbohydrate and urobilinogen metabolism, which he concluded to be evidence of derangement of the autonomic nervous system. The results of sympathectomy and ganglionectomy reported by Koch and de Savitsch [11] have also been interpreted to some degree as leading to these conclusions.

As a step toward answering this question a new series of experiments was set up in which the coagulation reactions of patients with disseminated sclerosis were studied as controls, against which were matched the reactions of patients with other diseases of the central nervous system. What is more important, such an investigation would determine whether the disorder in blood clotting is peculiarly characteristic of disseminated sclerosis, i. e., is not found in other diseases of the brain stem and spinal cord.

PROCEDURE

The subjects consisted of 10 patients with disseminated sclerosis and 10 patients with other diseases of the brain stem and spinal cord. These conditions included traumatic paraplegia, syphilitic amyotrophic lateral sclerosis, neurofibroma of the cord, chronic myelitis with paraplegia, spinal arachnoiditis, syringomyelia, Friedreich's ataxia, postencephalitic paralysis agitans and postpneumonic unilateral paralysis agitans. A patient having psychoneurosis with paraplegia was also included. The mean age of each group was 37 years.

The clinical diagnoses of the visiting neurologists were accepted, and patients for whom the diagnoses were doubtful were not included. The technics, as described later, were similar to those used by Simon and Solomon.[1]

The clotting time was estimated by a modification of the Howell method. By means of a tourniquet, blood was drawn from a vein of the arm into an oiled

9. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, New York, D. Appleton and Company, 1929, chaps. 9 and 10.

10. Haug, K.: Leberfunktionsprüfungen bei multipler Sklerose, Monatschr. f. Psychiat. u. Neurol. **88**:225 (April) 1934.

11. Koch, C. F., and de Savitsch, E.: Surgical Treatment of Disseminated Sclerosis by Sympathectomy and Ganglionectomy, Brit. M. J. **1**:1254 (June 11) 1938.

syringe. Care was taken to have the needle enter the vein directly in order to avoid the addition of tissue juices or air bubbles, either of which would lower the clotting time materially. A small amount of blood (from 0.5 to 1.0 cc.) was allowed to flow down the side of each of a series of fifteen small oiled test tubes. Every precaution was taken not to disturb the blood more than was necessary in transferring it from the vein to the tubes or thereafter. The test tubes, needles and syringes had been previously prepared by rinsing with a solution of 3 parts of ether to 1 part of liquid petrolatum. The tubes had been inverted and allowed to drain for approximately thirty minutes, in which time the ether evaporated, leaving a thin coating of oil on the glass. After the blood had been placed in the tubes, one tube was inverted every five minutes until clotting occurred. When a tube was inverted and it was found that the blood had not coagulated, the tube was discarded, since the disturbance thus produced is enough to make the blood clot more rapidly thereafter. When a tube was inverted and the blood was found to be clotted, the next two tubes were also inverted. If these likewise showed clotting, the time was called the end point. If either of the next two tubes did not show clotting, a plus-minus (±) rating was assigned to that time reading, and another tube was inverted five minutes later, and so on, until the end point was reached. This point was taken as the clotting time except when two or more plus-minus readings appeared in a series of determinations, when an average was taken for the clotting time. With this method normal subjects showed a clotting time ranging from twenty-five to forty-five minutes. The method was accurate to within five minutes. A change of less than ten minutes was not considered significant.

By the method described for determining the clotting time, two sets of experiments were conducted on each patient. In one a febrile condition was induced by the intravenous injection of typhoid vaccine. In the other the subcutaneous injection of epinephrine was used to obtain reactions simulating physiologic aspects of emotional excitement.

Determination of Coagulation Time After Intravenous Injection of Typhoid Vaccine.—In these experiments the first determination of clotting time was made at about 8 a. m., and the patient was then given an intravenous injection of 200,000,000 typhoid bacilli. Further estimations of clotting time were made two, five, eight, twenty-four, thirty-two, forty-eight, seventy-two and ninety-six hours later. On the first day the patient was not given food until after the eighth hour determination. On the second, third and fourth days breakfast was withheld until after the clotting time was estimated. The thirty-two hour determination was made before the patient was given supper. A chart showing the temperature every hour was kept during the course of the fever.

Determination of Coagulation Time After Subcutaneous Injection of Epinephrine.—The patient fasted throughout the period of the experiment. After the clotting time was first estimated, 1 cc. of a 1 : 1,000 solution of epinephrine hydrochloride was injected subcutaneously, and the clotting time was estimated one, two, three and four hours later. Medication was not permitted during any of the experiments. The patient was permitted to drink water but not to smoke. Excitement and emotion of any kind were guarded against as far as possible.

RESULTS

Effect of Intravenous Injection of Typhoid Vaccine on Coagulation Time.—Chart 1 shows the mean curve of the changes in coagulation

time after the injection of typhoid vaccine for the control subjects (with disseminated sclerosis) and for the subjects with other neurologic disorders. The separate readings for each of the subjects in the two groups are also given. Since the basal coagulation time varies in different persons, results are given in percentages of the basal coagulation time

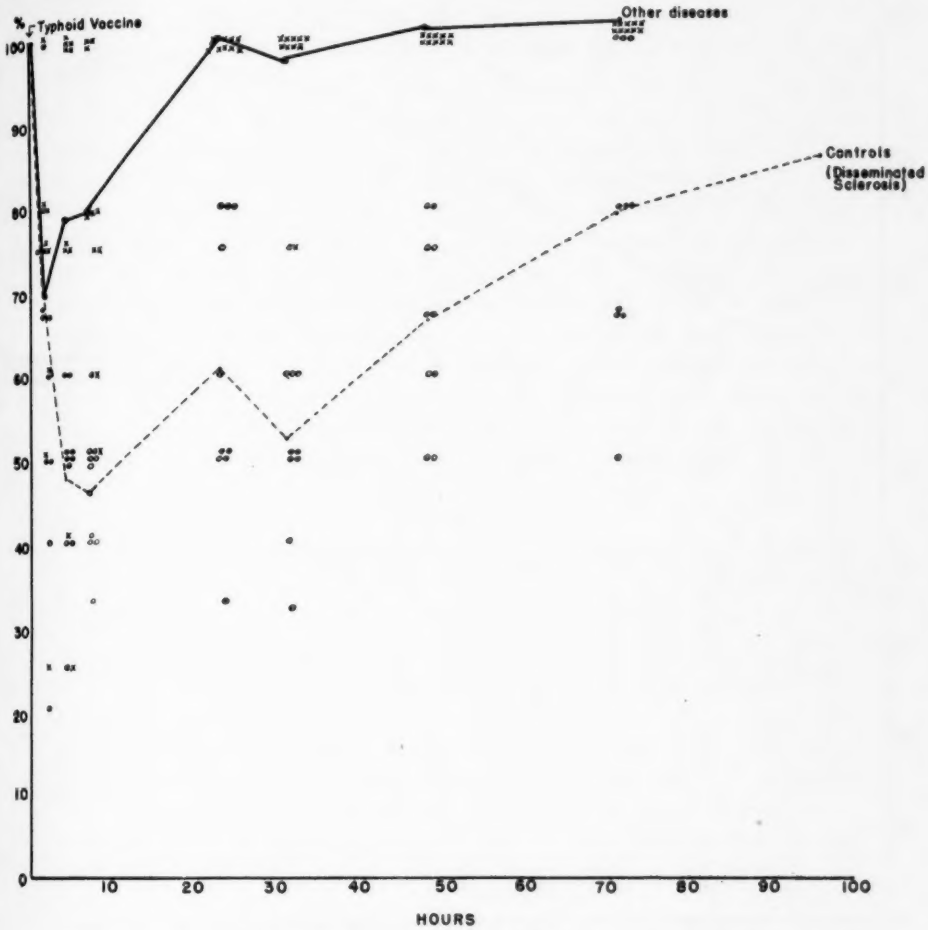

Chart 1.—Effect of the intravenous injection of typhoid vaccine on the coagulation time of the blood. The ordinate represents the percentage of the basal premedication coagulation time, and the abscissa, the time expressed in hours. The broken line is the curve of the mean coagulation time for the 10 patients with disseminated sclerosis, the individual cases being represented by *o*'s. The continuous line is the curve of the mean coagulation time for the 10 patients with other diseases of the brain stem and spinal cord, the individual cases being represented by *x*'s.

for each patient. The mean curves show that in patients with disseminated sclerosis the drop in coagulation time was prolonged from

seventy-two to ninety-six hours, as against twenty-four hours for patients with the other disorders. After four days the coagulation time had returned to the original level in only half the patients with disseminated sclerosis, while in all the patients with other disorders it returned to

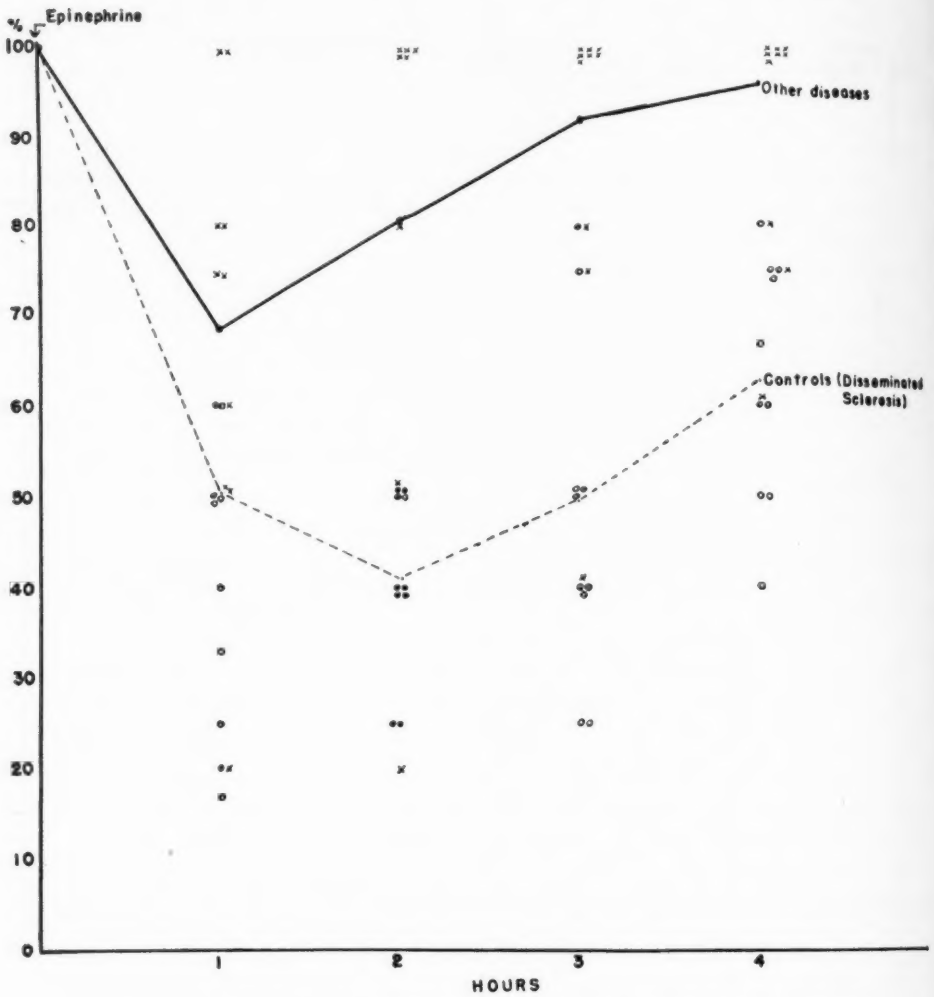

Chart 2.—Effect of the subcutaneous injection of epinephrine on the coagulation time of the blood. The ordinate represents the percentage of the basal premedication coagulation time, and the abscissa, the time in hours. The broken line is the curve of the mean coagulation time for the 10 patients with disseminated sclerosis, the individual cases being represented by *o*'s. The continuous line is the curve of the mean coagulation time for the 10 patients with other diseases of the brain stem and spinal cord, the individual cases being represented by *x*'s.

normal in twenty-four hours. The intensity of the change in clotting time was greater in the patients with disseminated sclerosis by 25 per cent. This change, while significant, was not as pronounced and individually consistent as the prolongation of the reduction in clotting time. All the patients with disseminated sclerosis gave the characteristic response described by Simon and Solomon.[1] The other patients responded "normally."

Effect of Subcutaneous Injection of Epinephrine on Coagulation Time.—These changes are indicated in chart 2 in the same manner as in chart 1. The difference in intensity of the reaction in the two groups was much more striking (40 per cent), while the duration of the reduction was still greatly prolonged in the patients with disseminated sclerosis. Individual variations, however, were more pronounced. While in all the patients with disseminated sclerosis the decrease in coagulation time was prolonged, as described by Simon and Solomon,[1a] 3 of the other patients showed a prolonged reaction, though for 2 of them the reduction was above the mean level for disseminated sclerosis. One of these patients, who had psychoneurosis with paraplegia, showed a return to only 60 per cent of his basal coagulation time after four hours. The other 2 patients, who showed returns to 75 and 80 per cent levels, had chronic myelitis and traumatic paraplegia, respectively.

COMMENT

It is readily observable that this study corroborates that of Simon and Solomon [1] in all respects. The greater response of all patients to epinephrine may be due to the use of a different product in England, with, perhaps, a different standardization. The general characteristics of the reactions were similar to those previously found. The location of a pathologic lesion in the brain stem or cord appears to have no relation to the changes in coagulation time. Though absolute proof has not yet been educed, the present study indicates that the change in coagulation time is associated with a particular disease, disseminated sclerosis, and probably precedes the onset of symptoms. In 1 of the cases of disseminated sclerosis with symptoms of three days' duration the characteristic blood changes were present. Further support is here found for the opinion expressed by Putnam [6] that the lesions of disseminated sclerosis are the result of intravenous thromboses effected through an abnormal lability of the blood-clotting mechanism. Putnam [5a] reported that an increase of fibrinogen was found in cases of disseminated sclerosis, and this may be related to disorders of the liver, as inferred by Haug [10] and Weil and Cleveland.[12] Brickner [13] suggested a possible relationship

12. Weil, A., and Cleveland, D.: A Serologic Study of Multiple Sclerosis, Arch. Neurol. & Psychiat. **27**:375 (Feb.) 1932.

13. Brickner, R. M.: Recent Experimental Work on the Pathogenesis of Multiple Sclerosis, J. A. M. A. **166**:2117 (Jan. 20) 1936.

between the lipolytic materials found in the blood of patients with multiple sclerosis and their potential activity on the erythrocytes to produce thrombi. In Brickner and Brill's [14] dietary studies on patients with multiple sclerosis many were found to have lived on queer diets for years before the onset of their disorder.

The possible relation of these dietary aberrations to disorders in the blood-coagulating mechanisms is not to be dismissed. That the critical thrombus-producing change in the blood takes place after a single stimulus, such as fever or shock, seems unlikely. In that case serious consequences could have been expected from the experiments reported. In 1 patient the effect of a repeated stimulus was tried. Two weeks after the first set of experiments (when the blood-clotting time had returned to nearly the first basal level) another injection of the vaccine was given. The response was so much more intense and prolonged than in the first series that further studies were dropped because of the potential danger to the patient.

On the whole, one may justifiably take the position stated by Rhodes: [15]

> Various agents, some being as yet unidentified, some viruses, some chemical substances, and some . . . bacteria, have the property of causing demyelinisation. Although some of these agents may cause demyelinisation by a direct action on the myelinated tissue itself, it is possible that others act by causing the blood to clot more readily, the resultant vascular thromboses producing the characteristic histological picture of demyelinisation.

SUMMARY AND CONCLUSIONS

The reaction of the blood coagulation time to the intravenous administration of typhoid vaccine and to the subcutaneous administration of epinephrine was studied in patients with disseminated sclerosis and in patients with other disorders of the brain stem and spinal cord.

To the administration of typhoid vaccine both groups of patients responded with a reduction in coagulation time, the drop being 25 per cent greater at maximum in disseminated sclerosis. The patients with disseminated sclerosis showed a prolongation of the reduction in clotting time three times as great as the patients with other disorders.

To epinephrine the responses were similar. The intensity of the response was 40 per cent greater at maximum in patients with disseminated sclerosis than in patients with the other disorders. The duration of the reduced coagulation time for disseminated sclerosis was more than twice that for the other diseases.

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14. Brickner, R. M., and Brill, N. Q.: Dietetic and Related Studies on Multiple Sclerosis, Arch. Neurol. & Psychiat. **46**:16 (July) 1941.

15. Rhodes, A. J.: Disseminated Sclerosis: A Review of Modern Work on Its Aetiology, Edinburgh M. J. **46**:581 (Sept.) 1939.

It is suggested that in disseminated sclerosis there is a constitutional or acquired disorder of the blood-clotting mechanism which makes it more sensitive to exogenous or endogenous stimuli which tend to reduce the blood coagulation time. Intensive or repeated stimulation of this oversensitive mechanism may lead to intravascular thrombosis under certain conditions.

The disorder of blood coagulation is characteristic of disseminated sclerosis and was not found in patients with the other diseases of the brain stem and spinal cord studied.

Connecticut State Hospital.

DISTRIBUTION OF ALKALINE PHOSPHATASE IN NORMAL AND IN NEOPLASTIC TISSUES OF THE NERVOUS SYSTEM

A HISTOCHEMICAL STUDY

HAROLD LANDOW, M.D.†

ELVIN A. KABAT, PH.D.
AND
WILLIAM NEWMAN, B.A.

NEW YORK

The histochemical method for demonstration of alkaline phosphatase introduced by Gomori [1] and by Takamatsu [2] has made possible the precise location of this enzyme in tissues and in individual cells in which it had not previously been found. Thus, phosphatase has been shown to occur in the epithelium of the small intestine, the proximal convoluted tubules of the kidney, ossifying cartilage, embryonic perichondrium, capillary endothelium and certain tumors, notably osteogenic sarcomas in the chicken and mouse and a fibroadenoma of the breast in man [3]. The information obtained has provided support for the hypothesis of Lundsgaard [4] that a phosphorylase-phosphatase system is important in the absorption of dextrose by the epithelium of the small intestine and in the reabsorption of dextrose in the proximal

† Dr. Landow died March 27, 1942.

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From the Departments of Neurology and Neuropathology, Columbia University College of Physicians and Surgeons, and the Neurological Institute of New York.

1. Gomori, G.: Microtechnical Demonstration of Phosphatase in Tissue Sections, Proc. Soc. Exper. Biol. & Med. **42**:23-26, 1939.

2. Takamatsu, H.: Histologische und biochemische Studien über die Phosphatase: I. Histochemische Untersuchungsmethodik der Phosphatase und deren Verteilung in verschiedenen Organen und Geweben, Tr. Jap. Path. Soc. **29**:492-498, 1939.

3. (*a*) Kabat, E. A., and Furth, J.: A Histochemical Study of the Distribution of Alkaline Phosphatase in Various Normal and Neoplastic Tissues, Am. J. Path. **17**:303-318, 1941. (*b*) Gomori.[1] (*c*) Takamatsu.[2]

4. Lundsgaard, E.: Hemmung von Esterifizierungsvorgängen als Ursache der Phlorrhizinwirkung, Biochem. Ztschr. **264**:209-220, 1933; Die Wirkung von Phlorrhizin auf die Glukoseresorption, ibid. **264**:221-227, 1933.

convoluted tubules of the kidney.[5] The question of the function of phosphatase in the other tissue cells has become of considerable significance.

No extensive studies of alkaline phosphatase in tissues of the nervous system have hitherto been undertaken. Gomori[1] stated that no phosphatase, or only traces of it, are found in nerve tissues. The enzyme has been found in the myelinated peripheral nerve of a chicken and in certain cells of the human adult pituitary gland, presumably the basophils; a perineural fibroblastoma was negative for phosphatase.[3a]

The present study was undertaken to determine more fully the distribution of alkaline phosphatase in normal and pathologic tissues of the nervous system, to obtain information about the role of this enzyme in the metabolism of nerve tissue and, finally, to evaluate the histochemical technic as a possible aid in the diagnosis of tumors and other pathologic changes affecting the nervous system.

METHOD

The method for the histochemical demonstration of phosphatase[6] is based on the deposition of calcium phosphate at the site of phosphatase action when a tissue section is incubated with sodium β-glycerophosphate at a p_H of 9 in the presence of calcium ions. An adjacent section serves as a control to determine whether any preformed calcium deposits are present. To insure maximum enzyme activity, the solutions contained one-hundredth molar magnesium sulfate, a concentration found to be optimal by Bodansky.[7] The detailed procedure described by Kabat and Furth[3a] was followed except for the following modifications: Tissues were incubated at 43 instead of 37 C. to obtain maximal phosphatase activity, the higher temperature having been determined empirically to give better results. In fixation of tissues it was found advisable to follow fixation in acetone or alcohol with twenty-four hours in dioxane (diethylene dioxide) before embedding.

In addition to the routine sections, "touch" preparations were made of a number of the tumors studied. The fresh tumor specimen was touched to a glass slide and the slide immersed for fifteen minutes in 95 per cent alcohol and incubated in the substrate for one hour, followed by exposure to ultraviolet light (von Kossa procedure) and a counterstain, such as hematoxylin and light green. Results obtained by this rapid technic could be correlated in all instances with those in the usual paraffin sections stained for phosphatase.

In another phase of the investigation, thick pyroxylin sections were prepared in order to study vascular architecture and arborization. Tissues were fixed in 95 per cent alcohol, followed by the usual procedure for embedding in pyroxylin,

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5. (*a*) Kritzler, R. A., and Gutman, A. B.: "Alkaline" Phosphatase Activity of the Proximal Convoluted Tubules and the Mechanism of Phlorhizin Glycuresis, Am. J. Physiol. **134**:94-101, 1941. (*c*) Kabat and Furth.[3a]

6. Gomori.[1] Takamatsu.[2]

7. Bodansky, O.: The Effect of Alpha Amino Acids and Magnesium on the Activity of Kidney and Intestinal Phosphatases, J. Biol. Chem. **115**:101-110, 1936.

and sections were cut in thicknesses ranging from 50 to 100 microns. The time of incubation in the substrate was reduced from two to one and a half hours, and the von Kossa procedure was shortened to fifteen minutes in most instances. These modifications in the technic helped to avoid excessive deposition of silver. The sections were counterstained with hematoxylin and light green and cleared. Various clearing agents were tried, including carbolxylene oil of cedarwood and oil of bergamot. The best results were obtained with oil of origanum.

No differences could be detected in the behavior of alkaline phosphatase toward dextrose-1-phosphate and creatine phosphate when these substrates were substituted for sodium β-glycerolphosphate.

DISTRIBUTION OF ALKALINE PHOSPHATASE IN NORMAL NERVE TISSUES

Mouse, cat, chicken and human nerve tissues were studied. Strong alkaline phosphatase activity was found in the leptomeninges and in the endothelium of blood vessels. Some activity was present in the parenchyma, the amount of reaction varying sharply in different species and in different portions of the nervous system.

Leptomeninges.—In all species studied the leptomeninges (fig. 1*A*) gave a strong reaction for alkaline phosphatase, the greatest enzyme activity being localized in the cytoplasm of the arachnoid cells. The leptomeningeal reaction was demonstrable at all levels of the nervous system, from the cauda equina to the optic sheath.

The pial vessels were positive for phosphatase, but the pial cells and the connective tissue fibers of both the pia and the arachnoid were negative. The arachnoid cells showed a pronounced phosphatase reaction, both at the surface and on trabeculae. The flat arachnoid cells seemed to be more heavily stained than those overlying the trabeculae. The external glial membrane for the most part showed staining for phosphatase, localized in astrocytic fibers.

Vascular Endothelium.—Marked phosphatase activity was demonstrable in the endothelial cells of the blood vessels throughout the nervous system; here, as in all other tissues, the enzyme was intracellular and cytoplasmic. Vessels of all sizes except large arteries showed staining of the endothelium. The fact that vascular endothelium gives a strong reaction for alkaline phosphatase makes the histochemical stain for phosphatase a uniquely effective method for outlining the vascular tree of any portion of the nervous system (fig. 1). By staining pyroxylin-embedded serial sections 50 to 100 microns in thickness for alkaline phosphatase, one may trace vessels to their smallest ramifications, demonstrate anastomotic relationships and obtain a clear picture of the richness of vascularization of any area. As a method of demonstrating vessels the phosphatase method has distinct advantages over Lepehne and Pickworth's modification of the benzidine technic, cited

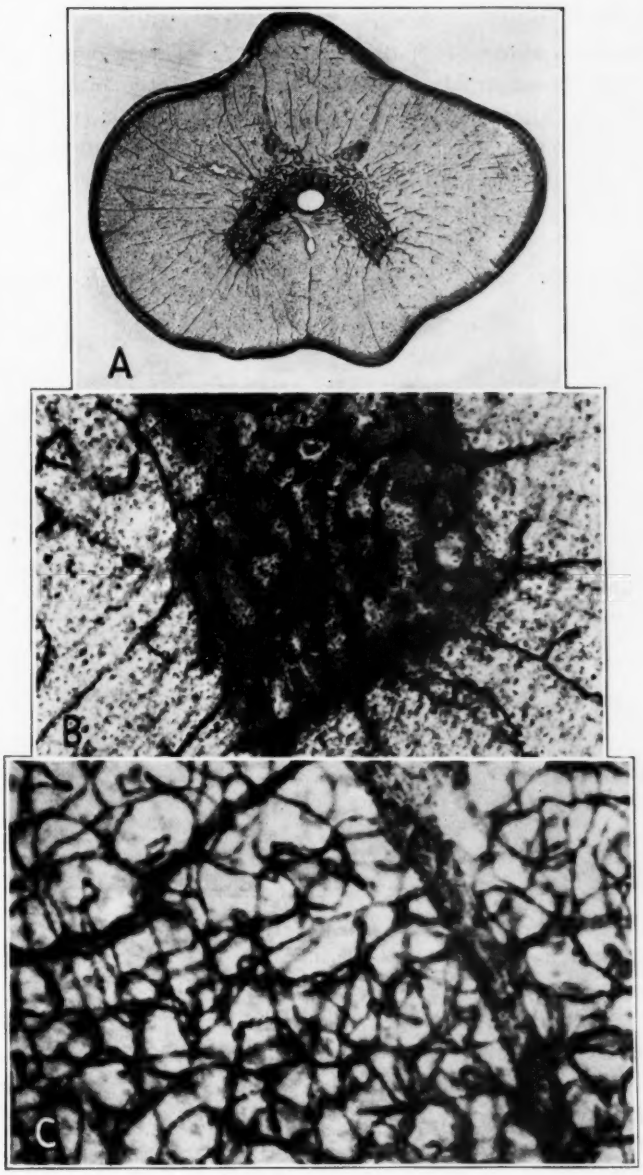

Fig. 1.—*A*, spinal cord of the cat, showing blood vessels and leptomeninges; thickness 75 microns. *B*, higher magnification of the anterior horn from the section shown in *A*. *C*, blood vessels in the frontal lobe of a cat brain; thickness 100 microns.

by Doherty and associates,[8] which demonstrates only vessels containing blood. In addition, the sections stained for phosphatase last indefinitely, whereas the benzidine preparations fade on exposure to light.

Parenchyma of the Brain and Spinal Cord.—The amount of phosphatase activity demonstrable in the parenchyma of the brain and spinal cord varied in different parts of the nervous system and in the different species studied, although in all forms except the chicken the parenchymal reaction was much less striking than that of the vascular endothelium and the arachnoid. The most notable parenchymal reaction for phos-

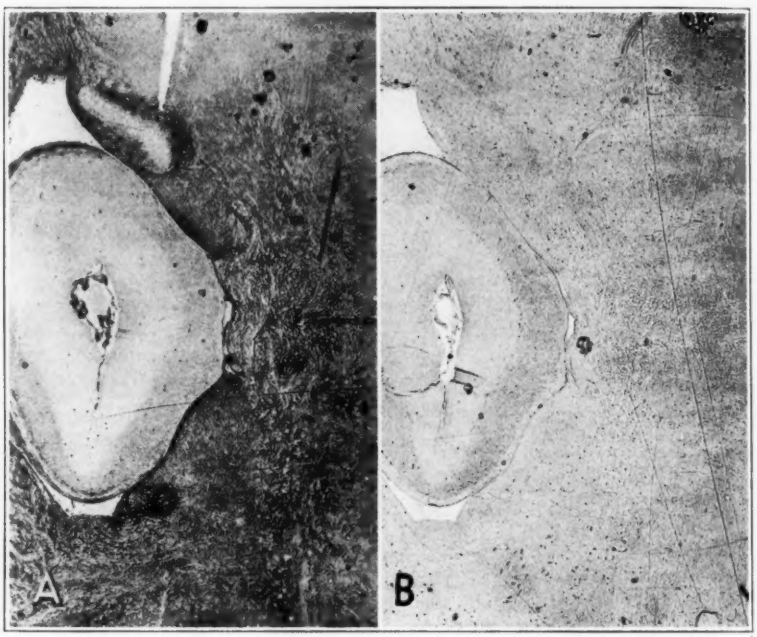

Fig. 2.—*A*, phosphatase in the parenchyma of the midbrain of the chicken. *B*, control section, not stained for phosphatase.

phatase was found in the chicken, where the brain stem (fig. 2*A* and *B*) showed especially intense but diffuse staining. The nerve cells of the chicken stood out unstained in the sections, while all intermediate structures were stained. Cerebellar folia showed similar diffuse staining of the molecular layer, but the nerve cells were negative for the phosphatase. The granular layer showed but a slight reaction, and its closely packed cells were negative. The white matter of the folia gave

8. Doherty, M. M.; Suh, T. H., and Alexander, L.: New Modifications of the Benzidine Stain for Study of the Vascular Pattern of the Central Nervous System, Arch. Neurol. & Psychiat. **40**:158-162 (July) 1938.

a moderate reaction, all structures being positive. The central white matter was deeply stained throughout. The nerve cells of the roof nuclei were unstained. In the cerebrum of the chicken staining was much less intense, but was heaviest in the diencephalon and in the corpus striatum. At times there were traces of staining in the cerebral cortex. The cerebral white matter was essentially negative.

In the human brain, the parenchyma gave a negative reaction, including areas of the medulla, thalamus, hypothalamus, cerebrum, cerebellum, caudate nucleus, putamen, globus pallidus, internal capsule and pons. Many corpora amylacea throughout the brain were positive

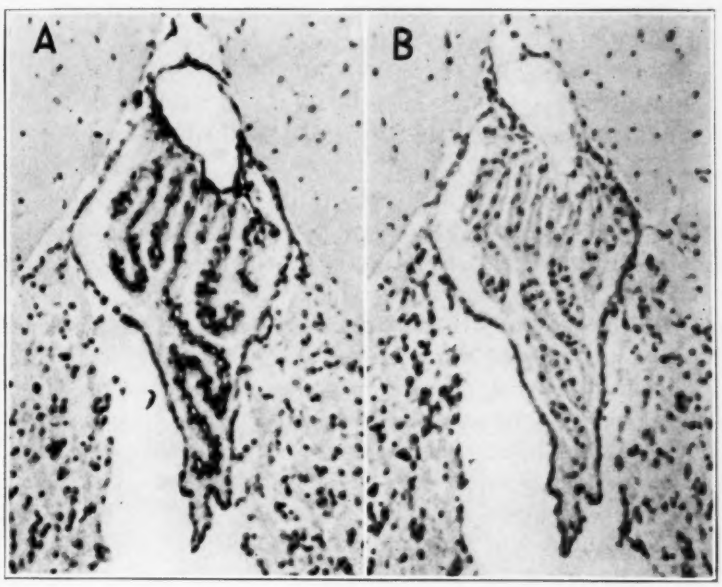

Fig. 3.—*A*, choroid plexus of the mouse. *B*, control section, not stained for phosphatase.

for the enzyme, particularly in the external glial membrane. Astrocytic fibers were also observed to contain phosphatase.

The mouse brain contained small amounts of phosphatase, with diffuse staining of the intercellular parenchyma. No phosphatase was noted in the corpus striatum, the pons or the cerebellar folia, and only traces were observed in the thalamus. Small amounts of phosphatase were present in the gray matter of the medulla and moderate amounts in the gray matter of the cord. The white matter in both regions and the nerve cells in general contained no phosphatase.

Ventricular System.—The ependymal cells lining the ventricles were uniformly negative for phosphatase.

The choroid plexus of the mouse, cat and man presented a striking appearance when stained for the enzyme; the endothelium of the capillary in the stroma of each villus was sharply stained, while the overlying ependymal cells were unstained (fig. 3*A* and *B*).

Cranial and Peripheral Nerves.—The optic nerves of the cat and man showed no phosphatase reactivity in the nerve fibers. The leptomeningeal sheath surrounding the optic nerve was well stained, as was the vascular endothelium. Sections of the sciatic nerve of the cat and of the human abducens nerve showed no reaction for phosphatase, except in the endothelium of blood vessels. The sciatic nerve of the chicken, however, gave a decided reaction for phosphatase, chiefly in what appeared to be the Schwann sheath. The axons and myelin sheaths were negative for phosphatase.

A sympathetic ganglion in the orbit showed no phosphatase in the neural tissue. Some capsule cells contained the enzyme and served to outline nerve cells. The sheath of the ganglion was stained.

PHOSPHATASE IN TUMORS OF THE NERVOUS SYSTEM

A group of common tumors of the nervous system was investigated, most of the material for study being obtained from patients at operation. Of the tumor types studied for phosphatase, the meningioma yielded the most strikingly positive results. A slight to moderate reaction for phosphatase was observed also in several astrocytomas and in 1 oligodendroglioma. In various other primary neoplasms of the nervous system the tumor cells consistently failed to give a reaction for phosphatase, although the enzyme was usually demonstrable in the endothelium of the blood vessels. (These observations must, of course, be interpreted with some caution, since only a small portion of the tumor was examined in any case and it is conceivable that there may be considerable variation in the amount of enzyme present in different portions of the same tumor, although in no instance was this observed to be the case).

Meningioma.—Of 11 meningiomas studied (fig. 4*A* and *B*), the tumor cells in 7 gave a strongly positive reaction for alkaline phosphatase, the enzyme being localized in the cytoplasm. The endothelium of the blood vessels of the tumor in general stained even more heavily for phosphatase than did the tumor cells. In 4 cases the tumor cells failed to give a reaction for phosphatase. In 3 of these at least part of the vascular endothelium contained the enzyme; in the fourth, in which the tumor had undergone extensive fibrosis and hyalinization, no phosphatase was demonstrable in the sections examined. In the cases in which the tumor cells gave a positive reaction for phosphatase the enzyme appeared to be distributed fairly uniformly throughout the sections, although there was some variation between individual cells and between groups of cells.

In the group of meningiomas there was a suggestive correlation between the presence of phosphatase activity and that of calcification in the tumor. Four of the 7 phosphatase-positive meningiomas had areas of calcification. None of the 4 phosphatase-negative meningiomas was calcified in the areas examined.

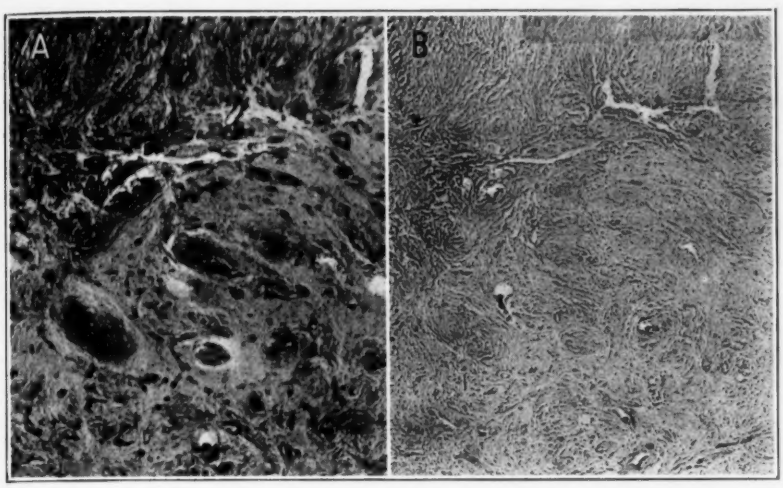

Fig. 4.—*A*, phosphatase in cells of a meningioma. *B*, control section, not stained for phosphatase.

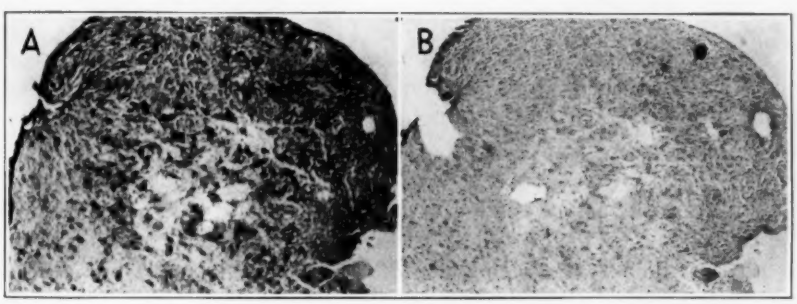

Fig. 5.—*A*, phosphatase in an astrocytoma. *B*, control section, not stained for phosphatase.

Astrocytoma.—Three of 4 astrocytomas (fig. 5*A* and *B*) studied gave a positive reaction for phosphatase. In 2 of these the enzyme appeared fairly evenly distributed throughout the sections; the reaction was more intense in the astrocytic processes than in the cell bodies, but both were stained. One tumor showed only light, spotty staining for phosphatase in the more fibrillar areas; the reaction of the fourth was negative. In all 4 astrocytomas the endothelium of at least some

of the vessels gave a positive response. The reaction for phosphatase in these tumors was less striking than that seen in most of the meningiomas.

Glioblastoma multiforme.—In only 1 of the 4 tumors of this type studied was a reaction for phosphatase obtained from the tumor cells; in this case the cells were rather heavily stained in several small areas, while the rest of the section was negative. Examination of an adjacent section stained with phosphotungstic acid hematoxylin suggested that the phosphatase was confined to astrocytic areas of the tumor. The endothelium of many of the vessels of this tumor contained phosphatase. In a second tumor phosphatase was demonstrated in the endothelium of a few vessels, the reaction of the remainder of the vessels and the tumor cells being negative. The sections of the other 2 tumors appeared entirely devoid of the enzyme.

Medulloblastoma.—Of 3 medulloblastomas studied for phosphatase, the tumor parenchyma of all was uniformly negative for phosphatase. In 2 of these the endothelium of the vast majority of the vessels gave a good reaction for phosphatase. In the third tumor, only a small fragment of which was available for study, the vessels gave no reaction.

Perineural Fibroblastoma (Schwannoma).—Of 3 tumors of this type which were studied for phosphatase, a moderate reaction was obtained in the vascular endothelium of 1; in the other 2 the vessels failed to stain. The tumor parenchyma was uniformly negative for the enzyme.

Oligodendroglioma.—Of 3 tumors of this type, the tumor cells of 1 gave a mild reaction for phosphatase in most areas. In this tumor many small plaques of calcification were scattered throughout the sections. In a second tumor no phosphatase was demonstrable in the tumor cell bodies, but the reticular material between the cells (cell processes [?]) gave a moderate reaction for the enzyme. There were a few small plaques of calcification in the sections. In a third tumor the cells were negative for phosphatase and no calcification was observed in any of the sections. In all 3 of the tumors studied the vascular endothelium gave a strong reaction for phosphatase.

DISTRIBUTION OF PHOSPHATASE IN MULTIPLE SCLEROSIS

Autopsy material was studied from a case of multiple sclerosis in which symptoms of the disease had been present for about twenty-five years. Plaques of demyelination were scattered widely throughout the central nervous system. Portions of tissues containing grossly visible plaques were removed from the cerebellum, the pons and the cerebrum. The Mahon stain for myelin was employed to outline the areas of demyelination, while an adjacent section was studied for phosphatase.

It was observed grossly that the plaque gave a reaction for phosphatase and that the brown areas of silver staining corresponded to demyelinated areas of the Mahon preparation. Microscopically there was a diffuse reaction for phosphatase throughout the plaque, varying somewhat in intensity in different areas. However, not all of the plaques displayed phosphatase activity. On examination of adjacent sections stained with phosphotungstic acid hematoxylin, it was apparent that the phosphatase activity was correlated with the amount of astrocytosis which had occurred, rather than with the degree of demyelination (fig. 6*A* and *B*). The vascular endothelium in the region of the sclerotic plaques still

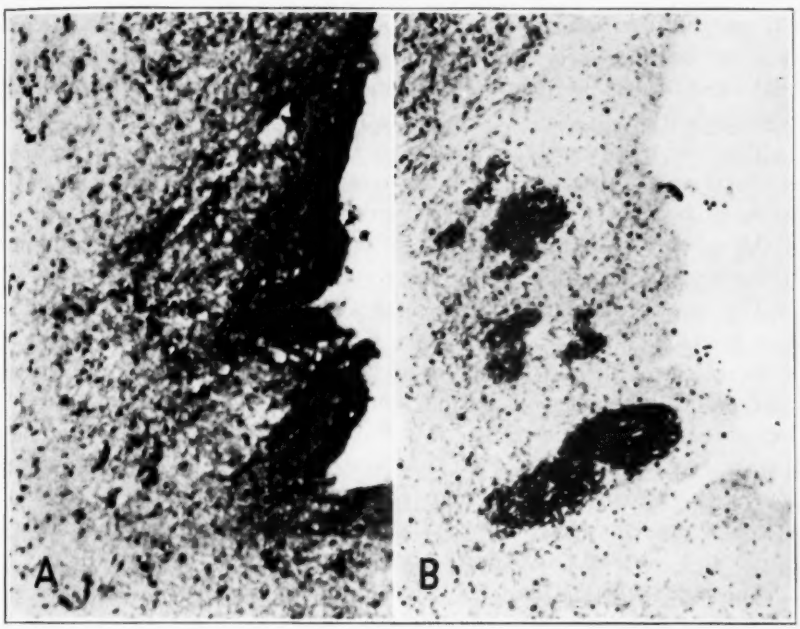

Fig. 6.—*A*, phosphatase in astrocytic areas of a plaque of multiple sclerosis; *B*, myelin stain of the same field as that shown in *A*, from an adjacent section.

showed phosphatase activity, so that vessels were sharply outlined. In the area of the plaques there was an apparent increase in the number of vessels as compared with the vascular density of normal zones.

COMMENT

In the studies of tumors of the nervous system two general tendencies were apparent: First, the cells of tumors tended to resemble their homologous normal cells in phosphatase activity. Thus, the meningioma cell, arising from the arachnoid, was often rich in phosphatase, as is the normal arachnoid cell. Astrocytomas, like areas of simple astro-

cytosis, might show moderate phosphatase activity. Second, it is noteworthy that the enzyme was demonstrable in tumors with a known tendency to calcification, and in some of these neoplasms calcification had actually occurred. This is exemplified by the presence of alkaline phosphatase in meningiomas, astrocytomas and an oligodendroglioma and the absence of the enzyme from the parenchyma of neurofibromas, medulloblastomas, pituitary adenomas and other ordinarily noncalcifying neoplasms. It is of interest that none of the phosphatase-negative meningiomas were calcified.

The blood vessels of the tumors studied often showed less phosphatase activity than was observed in vessels in normal nerve tissue, and many of the tumor vessels gave a negative reaction. The failure of these tumor vessels to stain for phosphatase may represent faulty vascular development or may reflect some deviation in tumor metabolism from the normal.

The role of phosphatase in the parenchyma of the nervous system is obscure. A basis for further investigation of this problem may reside in the fact that the parenchyma of the brain and sciatic nerve of the chicken, which has strong phosphatase activity, differs sharply in this respect from that in the other species studied.

The method of staining tissues for alkaline phosphatase is of value as a histologic technic, quite apart from the physiologic significance of the results. It should prove especially useful in studies of the vascular supply of the nervous system, and perhaps of other tissues as well, because of the complete picture it gives of the vascular tree. The phosphatase technic may be of some value in demonstrating pathologic changes in vascular endothelium; for this purpose ordinary paraffin sections are preferable to the thick pyroxylin preparations. The method should also be useful in studies of the arachnoid.

The method has a limited practical value in diagnosis of tumors, in which it should be used in conjunction with other histologic technics. The rapid modification of the technic, using "touch" preparations, which requires less than one and a half hours and gives results in agreement with those obtained with fixed and embedded preparations, should prove useful in fresh tissue diagnosis.

In connection with the tumor studies, the alkaline phosphatase activity of the serum and spinal fluid was determined in several patients having meningiomas and in several persons having no organic disease of the nervous system. In no instance was the serum phosphatase level elevated, nor was there more than a trace of phosphatase in the cerebrospinal fluid.

The regular occurrence of alkaline phosphatase in the vascular endothelium of the nervous system, and in the vessels of other organs as well, has important physiologic implications. It is conceivable, for

example, that the enzyme plays a role here similar to that ascribed to it by Lundsgaard [4] in the epithelium of the small intestine and the renal proximal convoluted tubules, where it is thought to be involved in the absorption of dextrose.[9] Although the transmission of dextrose through the capillary wall is generally regarded as simple diffusion along a concentration gradient, the presence of phosphatase in vascular endothelium suggests that phosphorylation and dephosphorylation may be involved in the passage of dextrose from the blood into the tissues. Studies to test this hypothesis are now in progress.

The phosphatase which is present in the arachnoid cells and the choroid plexus may subserve a function similar to that suggested for the vascular endothelium, namely, absorption of dextrose from the cerebrospinal fluid spaces.

SUMMARY

The distribution of alkaline phosphatase in normal and in pathologic tissues of the nervous system has been investigated, a method based on that developed by Gomori and by Takamatsu being utilized. The species studied included chicken, mouse, cat and man.

Pronounced alkaline phosphatase activity was present in the endothelium of the blood vessels of the central nervous system and in the arachnoid; the phosphatase activity in the parenchyma of the nervous system varied in different species and in different portions of the nervous system, the greatest activity being found in the brain stem of the chick. The cellular elements of the spinal fluid were negative for phosphatase.

Of the tumors studied, the phosphatase activity of the meningiomas was most striking. Moderate activity was present in several astrocytomas, in 1 oligodendroglioma and in astrocytic areas of 1 glioblastoma. In many tumors the parenchyma was negative for phosphatase, while the vascular endothelium was often positive. The vascular endothelium in the tumors was less constantly stained for phosphatase than that of the vessels of normal nerve tissue. Apparently the phosphatase content of tumors of the nervous system can be correlated roughly with (1) the phosphatase activity of the homologous normal tissue and (2) the tendency of the tumor to become calcified.

Phosphatase was present in areas of astrocytosis, such as the chronic plaques of patients with multiple sclerosis.

It is suggested that the phosphatase in vascular endothelium may play a role in the passage of dextrose through the capillary wall, similar to that suggested by Lundsgaard to explain the passage of dextrose through the intestinal wall and the proximal convoluted tubule of the kidney.

9. Kabat and Furth.[3a] Kritzler and Gutman.[5a]

The histochemical technic for phosphatase provides a uniquely effective method for demonstrating vessels, since it stains the vascular endothelium. By preparing thick serial pyroxylin sections and staining for phosphatase one may obtain a more complete picture of the vascular tree than that obtained by other methods. Studies of the vascular supply of various portions of the nervous system by this method are practicable.

The method has a limited usefulness in diagnosis of tumors when employed in conjunction with other technics.

Dr. Abner Wolf, of the department of neuropathology, assisted in interpreting the histologic observations. Dr. E. Herz took the photomicrographs.

Neurological Institute of New York.

A NEW TENDON STRETCH REFLEX

ITS SIGNIFICANCE IN LESIONS OF THE PYRAMIDAL TRACTS

VICTOR E. GONDA, M.D.
CHICAGO

In 1896 Babinski [1] described the reflex which bears his name, in two hundred and ninety-nine words. Two years later he [2] elaborated his work in two pages, presenting almost all the important features of the normal and pathologic plantar responses in human beings. Regarding this work Fulton and Keller [3] stated:

> As one reads it today in the light of clinical work of the last thirty years, it is evident that there is little to add concerning the mode of elicitation of the response and concerning its general characteristics except that the fanning of the outer toes is not mentioned.

However, Babinski [4] described the fanning in 1903. If one does not consider the extensive animal experiments of the last few years, one finds that little has been added to the essentials of these two short communications of Babinski, which have given more stimulus to clinical experimentation than the description of any other single sign in the field of neurology.

The Babinski sign is unparalleled in another feature; no other sign has so many modifications, all of which are only confirmatory. Indeed, the technics of Chaddock,[5] Oppenheim,[6] Gordon [7] and Schaefer,[8] to

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From the Department of Neurology and Psychiatry, Loyola University School of Medicine.

Read before the Chicago Neurological Society, Feb. 19, 1942 (with presentation of patients).

1. Babinski, A. J.: Sur le réflexe cutané plantaire dans certaines affections organiques du système nerveux central, Compt. rend. Soc. de biol. **3**:207, 1896.
2. Babinski, A. J.: Du phénomène des orteils et de sa valeur sémiologique, Semaine méd. **18**:321-322, 1898.
3. Fulton, J. F., and Keller, A. D.: The Sign of Babinski: A Study of the Evolution of Cortical Dominance in Primates, Springfield, Ill., Charles C. Thomas, Publisher, 1932.
4. Babinski, A. J.: De l'abduction des orteils, Rev. neurol. **11**:728, 1903.
5. Chaddock, C. G.: A Preliminary Communication Concerning a New Diagnostic Nervous Sign, Interstate M. J. **18**:742-746, 1911.
6. Oppenheim, H.: Zur Pathologie der Hautreflexe an den unteren Extremitäten, Monatschr. f. Psychiat. u. Neurol. **12**:518-530, 1902.
7. Gordon, A.: Paradoxic Flexor Reflex: Its Diagnostic Value, Am. Med. **8**:971, 1904.
8. Schaefer, M.: Ueber einen antagonistischen Reflex, Neurol. Centralbl. **18**: 1016-1018, 1899.

mention those most frequently used, do nothing more than elicit the Babinski reflex from another reflexogenic area. Except in persons with feet sensitive to touch, or because the soles are frozen, as occurred in soldiers during the first World War, or for other reasons which prevent the use of the original Babinski technic, these modifications do not aid in the original purpose: the diagnosis of involvement of the pyramidal tract. At best they merely verify it. It is now universally accepted that in the presence of lesions of the pyramidal tract all the responses supplementary to the correctly executed Babinski sign are less frequently and less pronouncedly elicitable. This is also true in primates with surgically produced lesions of the pyramidal tracts.[3]

The Rossolimo[9] and the Mendel-Bechterew[10] reflexes are quite different from the Babinski sign in their manifestations and in their essentials, although their significance is exactly the same. The Rossolimo and Mendel-Bechterew reflexes are tendon reflexes and manifest themselves in plantar flexion of the toes. Except in cases of multiple sclerosis, in which the Rossolimo sign is frequently observed, this and the Mendel-Bechterew sign are often absent in the presence of definite lesions of the pyramidal tracts.

The first tendon stretch reflex, signifying a lesion of the pyramidal tract, was discovered by Hoffmann. He demonstrated it to his students prior to 1904 but never published an account of his discovery.[11] It was first described by his pupil Curschmann,[12] who named it the Hoffmann sign.

For many years I have tried to apply the technic of Hoffmann to the lower extremities of human beings. The results at first were disappointing, inasmuch as any reflex response to this manipulation was less frequent than with the Babinski technic or its confirmatory methods. It was not until the advent of the electrically induced convulsive treatment that I secured more frequent responses by using a modified technic of firmly grasping the basal phalanx of the second toe and snapping it forcefully downward. With this method I[13] frequently obtained a prompt dorsiflexion of the big toe and flexion of the knee

9. Rossolimo, G. J.: Der Zehenreflex (ein speziell pathologischer Sehnenreflex), Neurol. Centralbl. **27**:452-455, 1908.

10. Mendel, K.: Ein Reflex am Fussrücken, Neurol. Centralbl. **23**:197-198, 1904. Bechterew, W.: Ueber einen besonderen Beugereflex der Zehen, ibid. **23**: 609-610, 1904.

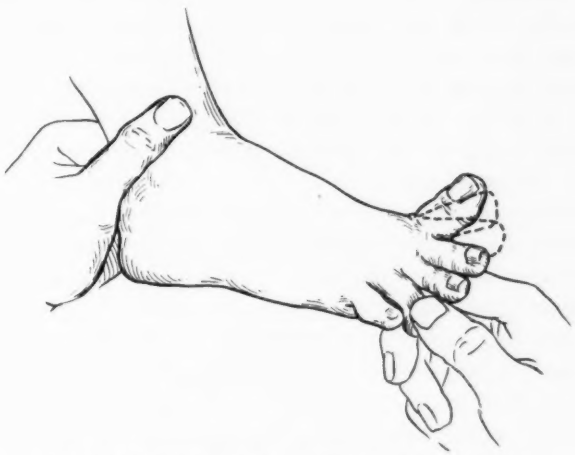
11. Bendheim, O. L.: Notes and Comments on the History of Hoffmann's Sign, Bull. Inst. Hist. Med. **5**:684-686, 1937.

12. Curschmann, H.: Ueber die diagnostische Bedeutung des Babinskischen Phänomenons in präurämischen Zustand, München. med. Wchnschr. **39**:2054-2057, 1911.

13. Gonda, V. E.: Treatment of Mental Disorders with Electrically Induced Convulsions, Dis. Nerv. System **2**:84-92, 1941.

and hip joints after the cessation of the convulsion. In the same paper in which I reported this work I mentioned that I had previously noted this new sign in cases of tumor of the frontal lobe and in 1 case of Friedreich's ataxia. I emphasized the fact that this sign was obtainable in cases of amyotrophic lateral sclerosis, in which the Babinski sign is frequently absent. I stated also that in cases of acute hemiplegia in which no other sign could as yet be demonstrated this was the only indication of involvement of the upper motor neurons.

I now wish to report further improvements in the technic. With them the new reflex seems to be a sensitive indicator of lesions in the pyramidal tracts. It is a tendon stretch reflex, but, in contradistinction to the Rossolimo and the Mendel-Bechterew sign, it manifests itself



Method of eliciting the new tendon stretch reflex.

in dorsiflexion of the big toe and at times, especially in babies, in fanning of the outer toes and even in flexion of the ankle, knee and hip joints, in a manner similar to the Babinski sign.

There are patients with severe spasticity of the lower extremities in whom the slightest stimulus evokes dorsiflexion of the big toe, no matter what technic is applied. In such persons the slightest downward bending or snapping of any of the outer toes, even without grasping their proximal phalanges, causes a quick dorsiflexion of the hallux. On the other hand, in persons in whom it is hard to obtain a reflex response, it may be necessary to grasp the distal phalanx of any of the outer toes, preferably the fourth, between the thumb and the index finger. Then the toe is flexed downward, describing the longest possible arc with considerable force, so as to stretch maximally the tendons of the toes. The toe is held in this position for six to eight

seconds in order to note a slow dorsiflexion of the big toe. At times, if after the toe is held in this position dorsiflexion of the hallux does not develop in approximately ten seconds, it may still be obtained by applying to the bent toe a sudden snap. On most occasions less stretch and less time than ten seconds suffice to elicit the reflex. There are a wide limit of time and a wide variation in responses. Between an outright, slow, long-lasting tonic dorsiflexion and a hardly perceptible flicker of the big toe there may be, indeed, many transitional manifestations of the same significance. Caution must be maintained not to confound voluntary toe movements with reflex responses. It takes considerable time and effort to master the technic and to evaluate the responses.

Some toes, especially those with distorted nails, are rather sensitive when the nails are squeezed between the finger tips. This objection can be overcome by holding the end phalanx just behind the nail and executing the recommended manipulations. At times one may observe an upgoing big toe when bending the outer four toes simultaneously downward. This manipulation has proved to be of great help in some doubtful cases.

The fanning of the outer toes and the withdrawal of the leg depend in some instances on the intensity of the applied stimulus. One may observe these concomitant movements when applying stronger stretch and miss them when the force is mild. Instead of fanning, one more frequently encounters, especially in adults, a quick, light dorsiflexion of the outer toes in connection with a definite dorsiflexion of the big toe. At times there is a short interval between the application of the stimulus and the ensuing reflex movements. Turning the head to one or the other side may increase the reflex on the "occiput side."

In testing several so-called healthy subjects who for all practical purposes did not suffer from involvement of the pyramidal tracts, I have never been able to elicit the new reflex, even in its most fragmentary form. It is not present in cases of pure striatal disease. I cannot state whether the reflex is present when there is a lesion of the anterior horn cells affecting only the flexor muscles of the toes and sparing the extensors, for in the last few years I have not met with such a lesion. On the other hand, I was able to obtain the new reflex in any case in which a lesion implicated the pyramidal tracts, even when the Babinski technic and all its modifications failed. I have had the opportunity of examining 12 patients with typical amyotrophic lateral sclerosis who showed plantar flexion of all the toes on plantar stimulation but reacted to the new technic with dorsiflexion of the big toe. Six patients with Friedreich's ataxia all showed the new sign, although only 1 of them manifested the Babinski sign. In 3 patients with

subarachnoid hemorrhage the new reflex was more constantly present than the sign of Babinski.

It is not necessary to enumerate all the diseases in which the pyramidal tracts are involved, but in cases of early combined degeneration of the spinal cord and in cases of encephalomalacia in which no Babinski sign can as yet be demonstrated the new sign can be elicited. These facts prove that the sign described in this paper is a more sensitive indicator of relatively small lesions of the pyramidal tracts and in cases in which the pyramidal and other tracts are simultaneously implicated than the signs used heretofore.

With the permission of Dr. P. C. Bucy, I examined 1 of his patients in whom he had surgically removed the left motor and premotor representations of the leg and arm areas, and I could easily demonstrate dorsiflexion of the right big toe on stretching the tendons of any of the outer toes.

At present I have under observation a Negress aged 39 who is suffering from a transection of the spinal cord at the second dorsal level caused by a knife stab and who lost all the reflexes below the injury. On the twenty-third day after her injury the first reflex movements appeared, which consisted of slight plantar flexion of the four outer toes in response to stroking the sole of her foot or to bending and snapping any of the outer toes. There was no reflex movement on any other manipulation. On the thirtieth day, in addition to flexion of the outer toes, the big toe showed plantar flexion when the Babinski or the new technic was applied. On the thirty-ninth day the new sign was elicitable.

The new reflex may be obtained on patients under general anesthesia induced by ether, ethylene or pentothal sodium. In patients with barbiturate poisoning, Cheyne-Stokes respiration and uremic coma it is also present. I have not been able to satisfy myself whether the new sign can be obtained during deep sleep, when, according to some observers, the Babinski sign is elicitable in a considerable proportion of healthy persons.

I found the optimum time for elicitation of the reflex after an electrically or a pharmacologically induced convulsion to be five to ten minutes after the last convulsive movement ceased. In persons in a postepileptic state it appears somewhat earlier. It can also be elicited during insulin coma.

In newborn babies, who react to plantar stimulation with a sudden withdrawal of the legs, it is hard to decide whether the first movement of the big toe is in the dorsal or in the plantar direction. This is the basis for a wide difference in opinion. Some have stated that the Babinski sign is practically never present in newborn infants and some

that it is elicitable in as high as 96 per cent.[14] The new reflex, which does not allow withdrawal of the leg, shows constant dorsiflexion of the big toe on bending the outer toes.

Through the cooperation of Dr. J. F. Fulton and Dr. M. A. Kennard, I have had the opportunity of examining a chimpanzee at the laboratory of neurophysiology of the Yale University School of Medicine. In this animal areas 4 and 6 (Brodmann) on the left side had been ablated two years previous to my examination. Right hemiplegia developed. The Chaddock, Oppenheim, Gordon or Schaefer sign could not be elicited. The Babinski sign was present, but was easily exhausted. The downward stretching of the outer toes resulted in constant dorsiflexion of the big toe with fanning of the four outer toes. At the same time and in the same laboratory, I tested a rhesus monkey the left hemisphere of which had been removed five weeks previous to my examination. This monkey did not show a Babinski sign or any of its modifications. It showed plantar flexion when the right sole was stroked.. Dorsiflexion of the right big toe was obtained when the new technic was applied.

SUMMARY

A new tendon stretch reflex and the technic of its elicitation are described. From clinical and experimental evidences it is concluded that this new reflex is more sensitive in indicating involvement of the pyramidal pathways than are the other reflexes that have previously been used for this purpose.

DISCUSSION

DR. ROY R. GRINKER, Chicago: The society is indeed fortunate in having this first exposition and demonstration of the new toe sign, which in the future should be designated as the Gonda sign. I do not know of any work that has been carried out with the same perseverance with which Dr. Gonda has investigated this problem. As long as I can remember I have seen him bending over toes trying to obtain the new sign. Those who have attempted again and again to elicit important signs of involvement of the upper motor neuron have been disappointed frequently in the Babinski sign; the difference between voluntary dorsiflexion and reflex dorsiflexion is puzzling. To obtain as early an indication of involvement of the descending motor tract as this method affords is of extreme significance. Since Dr. Gonda demonstrated the sign to me, I have tried to elicit it in many patients of my own, and I can say that what he has shown tonight can be confirmed in patients with known lesions. I hope other investigators will use this sign, with due recognition of the great credit that Dr. Gonda deserves.

DR. JOSEPH A. LUHAN, Chicago: I believe this sign is a distinct addition to the neurologist's diagnostic armamentarium. During the past few months I have examined all my patients by this method and have not elicited anything that I should call a false Gonda sign. In a few instances in which the plantar responses were plainly equivocal in patients with spastic weakness and other evidence of involve-

14. Chaney, B., and McGraw, M. B.: Reflexes and Other Motor Activities in Newborn Infants, Bull. Neurol. Inst. New York **2**:1-56, 1932.

ment of the pyramidal tract, I have elicited a distinct Gonda sign, thus confirming the presumption of pyramidal dysfunction.

DR. RICHARD B. RICHTER, Chicago: The response to this test is identical with that ordinarily elicited with the use of the Rossolimo technic, namely, stretching of the flexor tendons of the toes. It was of interest that the first patient's response to the conventional Rossolimo stimulus was extension rather than flexion. This is all rather contradictory, and I should like Dr. Gonda's comment on the nature of the response and why there is extension rather than flexion.

DR. R. P. MACKAY, Chicago: Has Dr. Gonda noticed that the ablation of area 4 produces a different response to this test than ablation of area 6, both in patients and in lower animals?

DR. PERCIVAL BAILEY, Chicago: I have used this maneuver for some years, since Dr. Gonda first demonstrated it to me, and have found it useful particularly for patients with tender soles, in whom it is sometimes difficult to elicit a Babinski sign.

DR. VICTOR E. GONDA, Chicago: Dr. Richter is mistaken when he believes that the response is identical with that of the Rossolimo reflex. With the Rossolimo technic shortening of the tendons takes place, whereas with mine the reverse, that is, lengthening, occurs. This probably accounts for the difference in responses. Tonight Dr. Richter obtained a false Rossolimo sign in the first patient who was presented, in whom the new reflex showed involvement of the pyramidal tracts, all the other well known signs being absent.

In reply to Dr. Mackay, the chimpanzee had areas 4 and 6 removed. Investigations will be continued by making isolated lesions in these areas. It may take years before there is a satisfactory solution to the problems involved. My hope is that, with this new and more sensitive technic, one may answer many questions which puzzle investigators, such as which signs indicate extrapyramidal cortical interruption and which the so-called pure pyramidal lesions.

25 East Washington Street.

CENTRAL NERVOUS SYSTEM IN VITAMIN E–DEFICIENT RATS

ABNER WOLF, M.D.
AND
ALWIN M. PAPPENHEIMER, M.D.
NEW YORK

During the past two years there have appeared numerous articles [1] dealing with the treatment of amyotrophic lateral sclerosis and other chronic degenerative diseases of the central nervous system with

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From the Departments of Neurology and Pathology, Columbia University College of Physicians and Surgeons.

1. (*a*) Bicknell, F.: Vitamin E in the Treatment of Muscular Dystrophies and Nervous Diseases, Lancet **1**:10, 1940. (*b*) Stone, S.: Treatment of Muscular Dystrophies and Allied Conditions: Preliminary Report on Use of Vitamin E (Wheat Germ Oil), J. A. M. A. **114**:2187 (June 1) 1940; Vitamin E in the Treatment of Muscle Disorders of Infancy and Childhood, J. Pediat. **18**:310, 1941. (*c*) Wechsler, I. S.: Recovery in Amyotrophic Lateral Sclerosis Treated with Tocopherols (Vitamin E), J. A. M. A. **114**:948 (March 16) 1940; The Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Tocopherols), Am. J. M. Sc. **200**:765, 1940; Further Progress in the Treatment of Amyotrophic Lateral Sclerosis with the Tocopherols (Synthetic Vitamin E), Tr. Am. Neurol. A. **66**:59, 1940; Amyotrophic Lateral Sclerosis Treated with Synthetic Vitamin E, J. Nerv. & Ment. Dis. **93**:353, 1941; Amyotrophic Lateral Sclerosis Treated with Synthetic Vitamin E, Arch. Neurol. & Psychiat. **45**:873 (May) 1941. (*d*) Sheldon, C. H.; Butt, H. R., and Woltman, H. W.: Vitamin E (Synthetic α-Tocopherol) Therapy in Certain Neurologic Disorders (with Negative Results), Proc. Staff Meet., Mayo Clin. **15**:577, 1940. (*e*) Ravina, A., and Plichet, A.: Le traitement des dystrophies musculaires (myopathies) et de la sclérose latérale amyotrophique par la vitamine E, Presse méd. **48**:886, 1940. (*f*) Weinberg, M. A., and Knoll, A. F.: Beneficial Effect on Amyotrophic Lateral Sclerosis Syndrome: Case in Which This Syndrome Was Precipitated by Sulphathiazole (Sulphanilamide Derivative), M. Rec. **152**:447, 1940. (*g*) Aguirre, M. R.: Use of Tocopherol Acetate, Synthetic Vitamin E, in Multiple Sclerosis and Amyotrophic Lateral Sclerosis, M. Bull. Vet. Admin. **17**:376, 1941. (*h*) Denker, P. G., and Scheinman, L.: Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Alpha-Tocopherol), J. A. M. A. **116**:1893 (April 26) 1941. (*i*) Ferrebee, J. W.; Klingman, W. O., and Frantz, A. M.: Vitamin E and Vitamin B_6: Clinical Experience in the Treatment of Muscular Dystrophy and Amyotrophic Lateral Sclerosis, ibid. **116**:1895 (April 26) 1941. (*j*) Viets, H. R.; Trowbridge, S. H., Jr., and Gunderson, T.: Therapeutic Use of Vitamin E in Amyotrophic Lateral Sclerosis, J. Nerv. & Ment. Dis. **94**:101, 1941. (*k*) Fitzgerald, G., and McArdle, B.: Vitamins E and B_6 in Treatment of Muscular Dystrophy and Motor Neuron Disease, Brain **64**:19, 1941. (*l*) Worster-Drought, C., and Shafar, J.: Motor

(Footnote continued on next page)

vitamin E in crude or purified form. These studies have been instigated by the currently accepted view that chronic vitamin E deficiency in rats brings about neurologic lesions more or less comparable to those found in human diseases. Since this is contrary to experience in this laboratory, we have undertaken anew a study of the question.

REVIEW OF LITERATURE

The first reference to possible alteration of neuromuscular function in cases of vitamin E deprivation is to be found in the paper of Evans and Burr,[2] in which is described paralysis of suckling rats born of vitamin E–deficient mothers. No study was made at that time of the underlying pathologic process. Material from such rats, however, was available to Lipschütz,[3] who (on the basis of Marchi preparations) described degenerative changes in (*a*) the crossed and homolateral, descending and ascending vestibular tracts, (*b*) the columns of Goll and Burdach and (*c*) the tectospinal tract. With Nissl preparations, it was possible to detect three or four stages of degeneration of the medioventral and lateral groups of anterior horn cells, which alone were affected—vacuoles, diffuse coloration of the cytoplasm and loss of the nucleolus and Nissl substance. As compared with preparations from a normal control rat of the same age, there was unquestionably great proliferation of the neuroglia.

Lipschütz attributed the paralytic symptoms in young rats entirely to these neurologic lesions, having failed to recognize the presence of severe changes in the skeletal muscle. The myopathic lesions which characterize this paralysis of suckling rats were first described by Olcott [4]

Neurone Degeneration Treated with Vitamin E, Lancet **2**:209, 1941. (*m*) Rosenberger, A. I.: Observations on the Treatment of Amyotrophic Lateral Sclerosis (Leucopoliomyelopathy) with Vitamin E, M. Rec. **154**:97, 1941. (*n*) Slaughter, R. F., and Cleckley, H.: The Treatment of Intrinsic Cord Disease with Vitamin E, J. M. A. Georgia **3**:106, 1941. (*o*) Doyle, A. M., and Merritt, H. H.: Vitamin Therapy of Diseases of the Neuro-Muscular Apparatus, Arch. Neurol. & Psychiat. **45**:672 (April) 1941. (*p*) De Jong, R. N.: Vitamin E and Alpha-Tocopherol Therapy of Neuro-Muscular and Muscular Disorders, ibid. **46**:375 (Dec.) 1941. (*q*) Mahoney, W. de G.: Neural Myatrophy and Vitamin E, South. M. J. **34**:389, 1941. (*r*) Harvey, R. W., and Hume, P. B.: Vitamin E and Nervous Disease, California & West. Med. **55**:293, 1941. (*s*) Meller, R. L.: An Evaluation of Vitamin E in the Treatment of Multiple Sclerosis and the Progressive Muscular Dystrophies, Journal-Lancet **61**:471, 1941. (*t*) Bang, J.; Einarson, L.; Fog, A. M., and Ringsted, A.: Treatment of Some Neuro-Muscular Diseases with Synthetic Vitamin E (Amyotrophic Lateral Sclerosis and Progressive Muscular Dystrophy), Nord. med. (Hospitalstid.) **10**:1201, 1941.

2. Evans, H. M., and Burr, G. O.: Development of Paralysis in the Suckling Young of Mothers Deprived of Vitamin E, J. Biol. Chem. **76**:273, 1928.

3. Lipschütz, M.: Les voies atteintes chez les jeunes rats manquant de vitamine E, Rev. neurol. **65**:221, 1936.

4. Olcott, H. S.: The Paralysis in the Young of Vitamin E Deficient Female Rats, J. Nutrition **15**:221, 1938.

in 1938 and later by Pappenheimer,[5] Barrie,[6] Verzàr,[7] Demole and Pfalz [8] and Telford, Emerson and Evans.[9] Olcott and Pappenheimer were unable to confirm Lipschütz' observations.

Undoubtedly, the most thorough study of the central nervous system in vitamin E–deficient rats is that of Einarson and Ringsted,[10] published in 1938. Their report has provided the experimental groundwork for the use of vitamin E in treatment of chronic nervous diseases.

Ringsted,[11] in 1935, had observed certain clinical abnormalities of gait and behavior in adult rats that had been kept on a vitamin E–deficient diet for a considerable time. He described four stages in the progression of the clinical symptoms.

1. Disturbances in gait, which became waddling and slightly incoordinated, followed by dragging of the hindlegs. There was some thinning of the fur over the posterior extremities.

2. Pronounced straddling of the hindlegs, with impairment in adduction of the thighs and distinct ataxia. The muscles of the hindlegs became atrophic; there were hypesthesia and hypalgesia.

3. Inability of the hindlegs to adduct. The animals could no longer jump into the cage. Muscular atrophy increased, and there was loss of hair, with appearance of bald spots.

4. Inability to walk; deformity of the hindfeet and toes, and lowered sensibility. Sometimes ulcerations appeared in the skin. The rats did not die in this stage as a result of the neurologic disturbance, even after twenty to twenty-four months on the diet.

The pathologic study of Einarson and Ringsted [10] dealt with older rats which had been maintained for various periods on a vitamin E–deficient diet.

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5. Pappenheimer, A. M.: The Pathology of Nutritional Muscular Dystrophy in Young Rats, Am. J. Path. **15**:179, 1939.

6. Barrie, M. M. O.: Vitamin E Deficiency in the Suckling Rat, Nature, London **142**:799, 1938.

7. Verzàr, F.: Der Kreatin-Stoffwechsel bei der Muskeldystrophie durch E Vitamin-Mangel und seine Beeinflussung durch Tocopherol, Ztschr. f. Vitaminforsch. **9**:242, 1939.

8. Demole, V., and Pfalz, H.: Neuromuskuläre Schädigungen von Jungtieren E- hypovitaminische Ratten, und ihre Behandlung mit synthetische Vitamin E, Schweiz. med. Wchnschr. **69**:123, 1939.

9. Telford, I. R.; Emerson, G. A., and Evans, H. M.: Histological Changes in Skeletal Musculature of Paralysed Suckling Young of E-Low Rats, Proc. Soc. Exper. Biol. & Med. **41**:291, 1939.

10. Einarson, L., and Ringsted, A.: Effect of Chronic Vitamin E Deficiency on the Nervous System and the Skeletal Musculature in Adult Rats, London, Oxford University Press, 1938.

11. Ringsted, A.: A Preliminary Note on the Appearance of Paresis in Adult Rats Suffering from Chronic Avitaminosis E, Biochem. J. **29**:788, 1935.

Two diets were used, which had the following percentage compositions:

	Diet II	Diet V
Caseinogen	20	20
Rice starch	53	68
Oxidized hardened lard	15	..
Dried brewers' yeast	7	7
Salt mixture (McCollum no. 185)	5	5
Vitamin A	40 I.U.* daily	40 I.U. daily
Vitamin D	2 I.U. daily	2 I.U. daily

* International units.

The animals were killed by bleeding from the carotid arteries. As a fixative a 1 : 10 dilution of neutral 40 per cent solution of formaldehyde was injected intraspinally; after removal of the internal organs, the body was placed in a solution of formaldehyde of the same concentration for one to two days, and the central nervous system was removed and fixed again in the solution of formaldehyde. The authors expressed distrust of the Marchi method, as used by Lipschütz, and stated that they obtained only "poor and inconstant pictures."

For myelin staining, Einarson and Ringsted used at first the Weigert-Kultschitsky and Wolter methods, but found application of the Spielmeyer method to frozen sections or of Weil's technic to paraffin and pyroxylin sections more satisfactory. For the study of changes in the ganglion cells the gallocyanin technic was preferred.

Their study disclosed lesions in the spinal cord, peripheral nerves and skeletal muscles. The first structures to be attacked were the proximal parts of the posterior roots and the proprioceptive, and probably also the uncrossed, paths in the fasciculus cuneatus and fasciculus gracilis. This phase of the degeneration corresponds to the end of clinical stages 1 and 2. There next appeared "beginning and increasing degenerative changes in motor cells of the anterior horns," increasing in severity in stage 3 and leading to progressive and, eventually, to extreme muscular atrophy and involvement of the corresponding peripheral nerves. It was doubtful whether the peripheral afferent fibers were affected; changes in the spinal ganglia were "relatively slight." In several animals with stage 3 of the disease partial degeneration of the corticospinal tracts was noted. No changes were present in the tectospinal or the bulbospinal tract or in the nuclei of the medulla or the metencephalon. Only in 1 animal were the cells in the deepest layers of the "precentral region" of the cerebral cortex degenerated.

As a rule, the "first and largest site of the process" was in the lumbosacral part of the spinal cord. The process gradually extended upward to the thoracic and the lower cervical portion of the cord as far as the fifth segment. In a few cases the cervical portion of the cord seemed to be most severely affected.

The anatomic picture thus resembled closely a combination of the lesions of tabes dorsalis and those of progressive muscular atrophy. In the few cases in which the pyramidal tract was affected, the lesions were stated by Einarson and Ringsted to be analogous to those of amyotrophic lateral sclerosis. The adductor muscles showed simple atrophy of the fibers and occasional increase in sarcolemma nuclei.

Monnier [12] in 1940 described alterations in the nervous system and striated muscles in adult rats maintained on a vitamin E–deficient diet. His material consisted of 38 adult rats which had been kept by Verzàr on a diet of starch, casein, lard, salts, cod liver oil and brewers' yeast. Symptoms were observed after nine or ten weeks and became progressively more severe. Ten of the animals died between the fourteenth and the twenty-third month, with a loss of weight of 40 to 70 Gm. in the final twelve days. The initial symptoms presented by the animals were *nevrosité*; blunting of "psychomotor reactions" in response to mechanical, olfactory and auditory stimuli, and difficulty in righting themselves and in maintaining their position on an inclined plane. After three or four months Monnier observed incoordination, tremor of the head, dysmetria and inefficiency in proprioceptive responses; general and localized sensory disturbances, with loss of sensitivity to pricking the tail or paws; diminution in olfactory or auditory sensation, and trophic or neurovegetative disturbances, such as exophthalmos, urinary incontinence, alopecia and ulcerations.

The following histologic changes were described. The skeletal muscles showed foci of segmental necrosis, multiplication of the sarcolemma nuclei and invasion of mononuclear elements in compact islets. The degenerative process became more severe and diffuse as the disease advanced. This was associated in its early stages with partial demyelination of the intramuscular branches of the peripheral nerves and with slight rarefaction of the posterior columns in the cord. Later Monnier observed severe degeneration, notably of the fasciculus of Goll, and hyperchromatism and sclerosis of the anterior horn cells. Contrary to the observations of Einarson and Ringsted, the pyramidal tracts were unaffected.

In this country similar studies were made on rats by de Gutiérrez-Mahoney and associates [13] in 1941. Young rats with paralysis, offspring of partially depleted mothers, and surviving rats born of depleted mothers and maintained for over a year on the vitamin E–deficient diet, and

12. Monnier, M.: Les altérations du système nerveux et des muscles striées chez le rat adulte carencé en vitamin E, Compt. rend. Soc. de phys. et hist. nat. **57**:252, 1940.

13. Gutiérrez-Mahoney, W.; Mason, K. E., and Swanson, H.: The Neuropathology of Vitamin E Deficiency in the Rat, Am. J. Physiol. **133**:308, 1941. Mahoney.[19]

comparable to the adult rats of Einarson and Ringsted, furnished material for this work. The ganglion cells were severely affected—hyperchromatism of the cytoplasm, with loss of Nissl substance, and thinning and elongation of the cell bodies, or a second type of change, characterized by diminution of stainable contents and vacuolation and phagocytosis, was observed. Both anterior and posterior horn cells, the nuclei of the medulla, the Purkinje cells, the large and small nerve cells of the dorsal ganglia and the cells of the cerebrum were affected. Myelin stains disclosed alterations in the sciatic nerves—swelling, fragmentation, ball formation and disappearance of myelin—and in the nerve endings of the muscle and skin. The anterior and posterior roots in the cauda equina and the long conducting pathways of the cord were also involved. Changes were observed in the anterior and lateral tracts, which in the rat represent the spinocerebellar and vestibulospinal connections, the posterior tracts and, to a less extent, the corticospinal pathways, the corona radiata and the median bundle of the forebrain. There was a pronounced glial reaction. Thus, the lesions described by de Gutiérrez-Mahoney and his associates were even more severe and widespread than those noted by Einarson and Ringsted.

MATERIAL AND METHODS

Diet I.—Vitamin E–deficient diet I was that used by Goettsch and Pappenheimer[14] in previous studies. It had the following percentage composition: commercial casein, 29.1; corn starch, 36.3; lard, 20.0; dried baker's yeast, 9.0; salt mixture, 3.6, and cod liver oil, 2.0.

During lactation the yeast content was raised to 16.6 per cent, and the other ingredients were modified accordingly. To insure the birth of living young a single dose of wheat germ oil was given at the beginning of pregnancy.

Controls.—One of the following diets was given.

1. A stock diet of pellets, the Rockland rat diet, containing ground yellow corn; ground hulled barley; ground hulled oats; ground whole wheat; soybean meal; meat scraps; powdered whole milk; alfalfa meal; sodium chloride, and calcium carbonate.

2. Diet X, a simplified complete diet, with the following percentage composition: whole wheat, 65.5; skimmed milk powder, 10; casein, 15; a product containing chiefly cottonseed oil (wesson oil), 5.0; cod liver oil, 2.0; calcium carbonate, 1.5, and sodium chloride, 1.0.

3. Diet I supplemented with tested wheat germ oil, 6 drops daily.

4. Diet I supplemented with 5 mg. of d-l-alpha tocopherol acetate weekly.

All the control rats showed normal growth and fertility, in contrast to those on the vitamin E–deficient diet, which were functionally sterile and showed the expected testicular degeneration.

14. Goettsch, M., and Pappenheimer, A. M.: α-Tocopherol Requirement of the Rat for Reproduction in the Female and Prevention of Muscular Dystrophy in the Young, J. Nutrition **22**:463, 1941.

We examined 19 rats maintained on diet I: 11 adult males, 4 adult females and 4 young. The adults were killed after periods ranging from one hundred and eighty to three hundred and sixty-five days. The control groups comprised 2 adult males maintained on the stock diet, 6 adult males fed diet X, 4 adult males which received a supplement of alpha tocopherol and 4 adult males which received 6 drops daily of tested wheat germ oil as supplement.

All the animals were killed with chloroform, and the brain, spinal cord and sciatic nerves were removed at once and treated as follows: in the majority of instances the spinal cord, brain stem, cerebellum and cerebrum were sectioned fresh in serial blocks. Two series of blocks were fixed in a 10 per cent concentration of solution of formaldehyde U. S. P., one series in 95 per cent alcohol and one in Zenker's solution. One of the two series of blocks fixed in the solution of formaldehyde, U. S. P. was further mordanted in preparation for the Pal-Weigert stain and pyroxylin embedding. The second set was embedded in paraffin, and the sections were stained by the Mahon method for myelin sheaths, by the Bodian method for axons, with cresyl violet for Nissl substance and with hematoxylin and eosin. The material fixed in 95 per cent alcohol was embedded in pyroxylin and stained with toluidine blue for Nissl substance. Sections from the Zenker-fixed blocks were stained by Mallory's phosphotungstic acid hematoxylin stain. Of the remaining rats, the brain and spinal cord were fixed in toto in a 10 per cent concentration of solution of formaldehyde U. S. P. and in from five to ten days were sectioned further, as previously described, and refixed in the special solutions. The same stains were used.

Sections of striated muscle and viscera were fixed in Zenker's solution.

HISTOLOGIC OBSERVATIONS

Nervous System.—No changes were observed in the appearance of the central nervous system or in the peripheral nerves in the vitamin E–deficient group as compared with the four control groups.

Anterior Horns of the Spinal Cord: The anterior horn cells at all levels were normal in number, size, contour and content of Nissl substance. They showed no diffuse hyperchromatism, such as has been described by others. In some instances in which it appeared at first that such hyperchromatism existed, further decolorization disclosed normal structure (fig. 3*A*). This was true for normal and for vitamin E–deficient rats (fig. 3*B*). Vacuolation of the cytoplasm of the anterior horn cells was not seen in any of the vitamin E–deficient animals. In 1 rat which had received the wheat germ oil supplement a few vacuolated cells were seen. This animal, which was killed at the end of six months, had had two fertile matings but at death showed no motile spermatozoa and many atrophic testicular tubules. In the absence of visceral lesions, the cause of this abnormality was not evident. Since the wheat germ oil was of known activity, it was probably not vitamin E deficiency. There was no reaction of the glia.

Nerve Roots: Except for occasional changes, clearly artefact, the nerve roots were normal (figs. 1*B* and 2*A*).

Columns of Goll and Burdach: None of the rats showed demyelination or loss of axons in these tracts in adequately stained Pal-Weigert preparations (figs. 1 and 2). At its cephalic extremity the column of Goll became less compact, but this was seen in both the deficient and the normal animals.

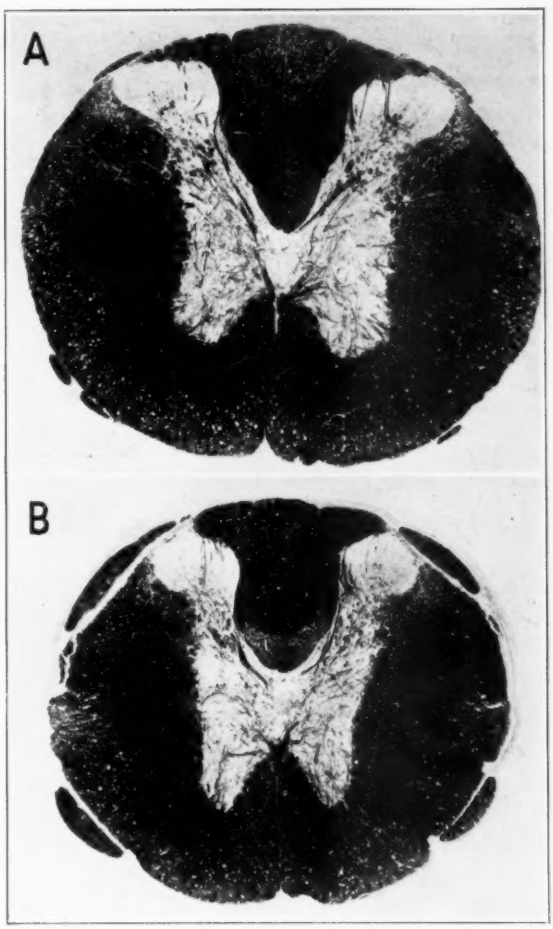

Fig. 1.—*A* (rat 329), age 227 days; final weight 268 Gm.; diet I, deficient in vitamin E; no supplement. Three sterile matings. Testes: weight 0.982 Gm.; 90 per cent of tubules atrophic. Cervical portion of cord (high segment): normal tracts and nerve roots. Pal-Weigert stain. *B* (rat 322), age 227 days; final weight 263 Gm.; diet I, deficient in vitamin E; no supplement. Seven sterile matings. Testes: weight 1.261 Gm.; no motile spermatozoa; complete loss of spermatogenesis. Thoracic portion of cord (high segment): normal tracts and nerve roots; partial myelination of corticospinal tract. Pal-Weigert stain.

Corticospinal Tract: The axons and myelin sheaths were intact in all rats (figs. 1 and 2).

Peripheral Nerves: The peripheral nerves were also observed to be normal in all animals.

Cerebral Cortex: Scattered shrunken, deeply staining nerve cells were present in both the deficient and the control animals.

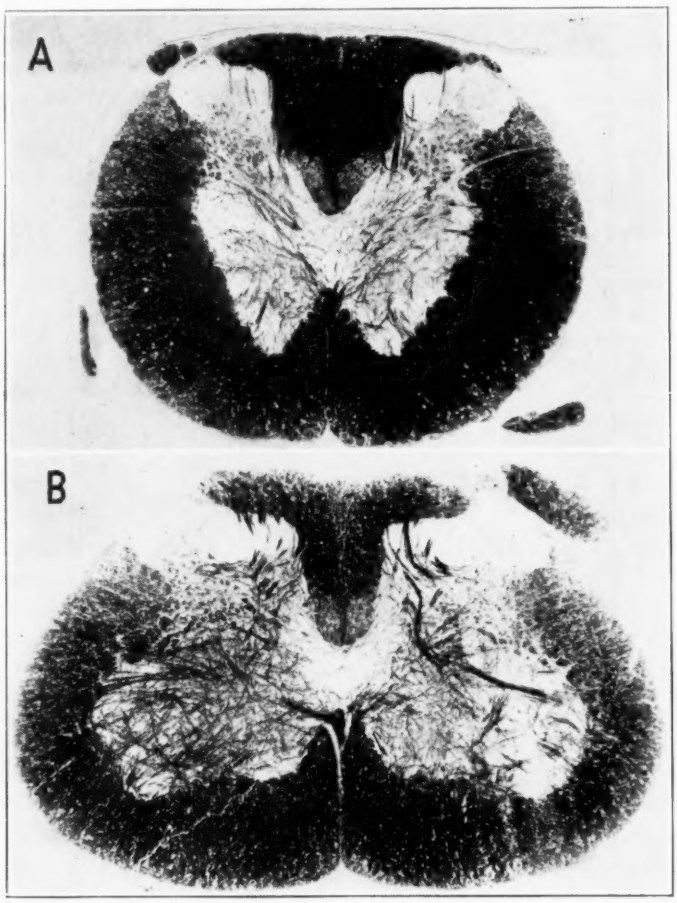

Fig. 2.—*A* (rat 329 [fig. 1 *A*]), thoracic portion of cord (low segment): normal tracts and roots; partial myelination of corticospinal tract. The rarefaction at the margin of one lateral column is obviously an artefact. *B* (rat 322 [fig. 1 *B*]), lumbar enlargement: normal tracts and roots. Pal-Weigert stain.

Other Nerve Structures: Particular attention was paid to other structures which certain authors have observed to be affected, namely, the crossed and the homolateral, descending and ascending vestibular

tracts, the tectospinal tract, the spinocerebellar tract, the corona radiata and the median bundle of the forebrain (de Gutiérrez-Mahoney), the nerve cells in the nuclei of Bechterew and Deiters (Lipschütz), the posterior horn cells, the nuclei of the medulla, the Purkinje cells and

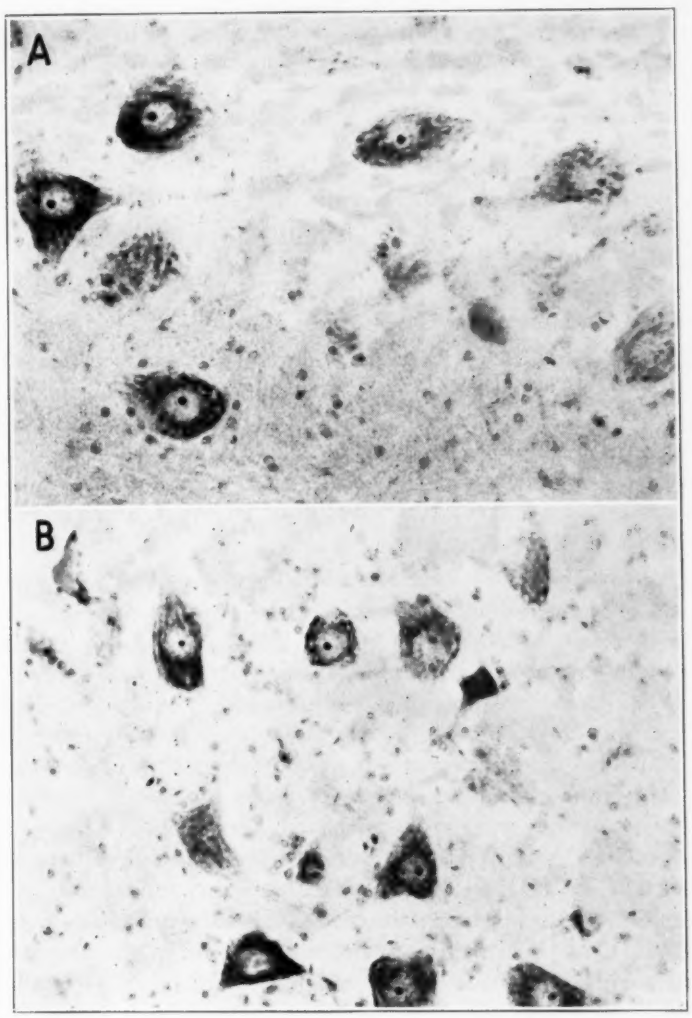

Fig. 3.—*A* (rat 324), age 6 months; weight at death 207 Gm.; diet I. Eight sterile matings. Testes: weight 0.506 Gm.; no motile spermatozoa; complete loss of spermatogenesis; normal anterior horn ganglion cells. Nissl stain; pyroxylin embedding; toluidine blue. *B* (rat 325), age 388 days; weight at death 368 Gm.; diet I plus 6 drops of wheat germ oil daily. Fertile matings. Testes: weight 3.60 Gm.; motile spermatozoa; active spermatogenesis. Spinal cord (lumbar enlargement): normal anterior horn ganglion cells. Note two shrunken hyperchromatic cells.

the nerve cells of the cerebrum. All these structures in our material were normal.

Skeletal Muscles.—In agreement with other investigators, we observed hyaline necrosis of scattered muscle fibers with cellular reaction in rats fed a vitamin E–deficient diet. It was absent in the protected rats. The lesions in older rats were minimal as compared with those associated with the paralysis of sucklings.

COMMENT

The discrepancy between our observations and those of Lipschütz, Einarson and Ringsted, Monnier and de Gutiérrez-Mahoney and his associates must be attributed to (1) differences in the strains of rats, (2) differences in diet and the possibility of a deficiency in factors other than vitamin E, (3) differences in technical procedures or (4) differences in interpretation.

Differences in Stain.—As to the importance of this factor we have no definite knowledge, although it is known that individual animals differ in their requirement for vitamin E. Since there has been general agreement as to the minimal protective dose required for the successful completion of pregnancy and for the protection against muscular dystrophy in sucklings regardless of strains, it seems unlikely that this factor explains the divergent results.

Differences in Diet.—Einarson and Ringsted's diet V was extremely low in fat. It was found, however, that the addition of oleic or linoleic acid, in addition to 50 mg. of peanut oil daily, did not prevent the appearance of paresis. It would appear, then, that the deficiency in fat is not the explanation for the discrepancy.[15] The diets used by Lipschütz and by de Gutiérrez-Mahoney were practically identical with those employed in this laboratory, with the exception of the salt mixture.[16] If dietary differences are responsible, they must be of a subtle nature which at present eludes analysis.

Controls: None of the experiments previously reported included a detailed study of litter mates which were maintained on the same diet supplemented with alpha tocopherol. Einarson and Ringsted used as controls rats which were given wheat germ oil; the wheat germ oil was then withdrawn from all but 1 animal, and the deficient diet was continued over a considerable period. Since paresis developed in these animals they cannot be regarded as controls. Control animals referred to in other papers have been maintained on stock diets. Before lesions

15. It is interesting that Einarson and Ringsted found that the disease developed less rapidly when oxidized lard was given. It has been the general experience that a diet with a high lard content favors the destruction of vitamin E.

16. De Gutierrez-Mahoney and associates used the Wesson modification of the Osborne-Mendel salt mixture, and Goettsch and Pappenheimer, the Hawk-Oser mixture.

are attributed to deficiency of vitamin E, controls should be studied in which the addition of this factor is the only variable.

Differences in Technic.—Fixation of Nerve Tissue: Einarson and Ringsted injected a 1:10 dilution of 40 per cent solution of formaldehyde into the spinal canal and along the sheaths of the sciatic nerves as a preliminary fixative and followed this with evisceration and immersion of the remaining carcass in the solution of formaldehyde. We followed this procedure in 1 case and found that it did not lead to the production of artefacts.

Traumatization of Tissue During Removal and Blocking: In our experience, it is easy to produce artefacts in the marginal portions of the tracts of the spinal cord and in the nerve roots by angulation and squeezing. The changes thus produced at times simulate demyelination of the tracts. When such blocks are cut more deeply at a distance from the traumatized tissue, the artificial nature of these changes becomes apparent.

Staining: Overstaining of anterior horn cells, both in vitamin E–deficient and in normal animals, may produce an appearance of hyperchromatism, which may be difficult to distinguish from that pictured in the paper referred to (Einarson and Ringsted, figures 48 and 49, pages 85 and 86). Further decolorization and the use of a number of Nissl technics with material embedded both in pyroxylin and in paraffin made evident the artificial nature of this "hyperchromatism" in our preparations.

The occurrence of shrunken, hyperchromatic ganglion cells in the cerebral cortex was a constant feature in both the deficient and the control rats. We have observed the same changes in the cortex of rodents studied in the course of routine experimental work and regard it as a frequent fixation artefact. According to Jakob,[17] so-called pyknomorphic forms of nerve cells are frequently observed in formaldehyde-fixed preparations, and Gurewitsch and Bychowsky[18] stated that these sclerotic-appearing ganglion cells are normal.

Myelin Sheath Stain: Two groups of myelin stains were used in this laboratory, those in which the iron salts are employed as a mordant (Spielmeyer; Weil; Mahon) and those in which mordanting is carried out by means of chromium and copper salts (Weigert; Pal-Weigert; Kultschitsky-Pal). The latter methods, although more time-consuming, have consistently proved more reliable, as has been noted by others. With the possible exception of the Mahon stain, the iron-mordanting methods have frequently given rise to artefacts which have the appearance of irregular areas of demyelination. This is particularly true of the Weil method. Preparations stained by an iron-

17. Jakob, A.: Normale und pathologische Anatomie und Histologie des Grosshirns, Leipzig, Franz Deuticke, 1927.

18. Gurewitsch, M., and Bychowsky, G.: Zur Architektonik der Hirnrinde (Isocortex) des Hundes, J. f. Psychol. u. Neurol. **35**:283, 1928.

mordanting method (Mahon) at times showed apparent demyelination, when Pal-Weigert preparations of adjacent segments of the same cord presented normally myelinated tracts.

Marchi Method: This method is notoriously capricious; its use, unsupported by other methods, is open to objection.[19]

Many discrepancies appear in previous reports of lesions in the nervous system and muscles. Reference to the table shows a lack of

Degenerative Lesions Reported in Rats

Author	Brain	Spinal Cord	Peripheral Nerves	Muscles	Staining Methods
Lipschütz (1936)		Crossed and homolateral, descending and ascending vestibular tracts; columns of Goll and Burdach; tectospinal tract; medioventral and lateral groups of anterior horn cells	Not examined	Not examined	Marchi stain
Einarson and Ringsted (1938)	Sclerosis of pyramidal cells (suggested as associated with changes in pyramidal tract)	Proximal portion of posterior roots; fasciculi cuneatus and gracilis; anterior horn cells; corticospinal (pyramidal) tract (in a few animals)	Sciatic nerve (in late stages)	Atrophy of neural type	Spielmeyer and Weil stains for myelin sheaths
Monnier (1940)		Posterior column, notably the column of Goll; hyperchromatism and sclerosis of anterior horn cells; pyramidal tracts unaffected	Partial demyelination of intramuscular branches	Foci of segmental necrosis and cellular infiltrations, multiplication of sarcolemma nuclei; progressive lesions	Iron hematoxylin stain for myelin sheaths (particular stain not mentioned)
de Gutiérrez-Mahoney (1941)	Ganglion cells of medullary nuclei; Purkinje cells; "large and small cells of the brain"; corona radiata; median bundle of forebrain	Anterior horn cells; posterior horn cells, dorsal root ganglion; anterior and posterior roots in cauda equina; spinocerebellar tract; vestibulospinal tract; "posterior tract"; corticospinal tract	Sciatic nerves; nerve endings of muscle and skin	Not described but reference to "muscle atrophy" in discussion	Kultschitsky and Spielmeyer methods and 1 per cent osmic acid for myelin sheaths; Marchi stain
Olcott (1938)	No lesions	No lesions	No lesions	Severe degenerative lesions	Marchi stain

uniformity in the observations of the various investigators. Olcott found no lesions in the nervous system in young rats; all the others noted degenerative changes in the columns of Goll and Burdach and in the anterior horn cells but differed as to what other structures were affected. Thus, while Einarson and Ringsted and de Gutiérrez-Mahoney observed degeneration of the corticospinal tract in the late stages, Lipschütz and Monnier specifically stated that this tract was unaffected. In this connection, it is interesting to note that there is

19. For a detailed discussion of the various artefacts which are readily produced in the preparation of Marchi sections, see Mettler, F. A.: Stain Technol. **7**:95, 1932.

a difference of opinion as to the degree of myelination of the corticospinal tract in the normal adult rat. Whereas Ranson [20] described it as only partially myelinated, Einarson and Ringsted asserted that it was completely myelinated. We have often noted that in iron hematoxylin preparations this tract stains uniformly, giving the impression of a completely myelinated tract, whereas a section from a contiguous block stained by the Pal-Weigert method will show only partial myelination. We therefore agree with Ranson that the picture seen in some of the iron hematoxylin stains is due to artefact, namely, staining of glial processes. Under these circumstances, errors of interpretation seem possible.

While Lipschütz and de Gutiérrez-Mahoney both observed changes in the vestibulospinal tracts, Lipschütz, in addition noted that the ascending vestibular and the tectospinal tracts were affected. De Gutiérrez-Mahoney, on the other hand, described degeneration of the spinocerebellar tracts. Einarson and Ringsted and Monnier saw no changes in any of these tracts. De Gutiérrez-Mahoney saw lesions in the brain stem, cerebellum and cerebrum, which have not been described by any of the other authors.

Similar discrepancies are found in the descriptions of the muscle lesions. Lipschütz and de Gutiérrez-Mahoney appear not to have included the skeletal muscles in their study. Einarson and Ringsted interpreted their lesions as indicating neural, rather than primary, atrophy, although some of their illustrations (figs. 51 and 74 of their study) appear to show evidence of actual destruction of individual fibers such as have been described in older rats by Burr, Brown and Mosely,[21] Evans, Emerson and Telford,[22] and Knowlton and Hines.[23]

To what extent these discordant observations should be ascribed to dietary differences and to what extent to variations in technic or interpretation or to lack of adequate control material is difficult to decide.

CONCLUSIONS

Under the experimental conditions obtaining in our laboratory, lesions of the central nervous system did not occur in vitamin E–deficient rats at any age.

630 West One Hundred and Sixty-Eighth Street.

20. Ranson, S. W.: The Fasciculus Cerebrospinalis in the Albino Rat, Am. J. Anat. **14**:411, 1914.

21. Burr, G. O.; Brown, W. R., and Mosely, R. L.: Paralysis in Old Age in Rats on a Diet Deficient in Vitamin E, Proc. Soc. Exper. Biol. & Med. **36**:780, 1937.

22. Evans, H. M.; Emerson, G. A., and Telford, I. R.: Degeneration of Cross Striated Musculature in Vitamin E-Low Rats, Proc. Soc. Exper. Biol. & Med. **38**:625, 1938.

23. Knowlton, G. C., and Hines, H. M.: Effect of Vitamin E Deficient Diet upon Skeletal Muscle, Proc. Soc. Exper. Biol. & Med. **38**:665, 1938.

SIGNIFICANCE OF INSULIN INHIBITION BY BLOOD OF SCHIZOPHRENIC PATIENTS

MARTIN G. GOLDNER, M.D.
AND
HENRY T. RICKETTS, M.D.
CHICAGO

Experiments indicating the presence of an anti-insulin substance in the blood of patients with schizophrenia have been presented by Meduna, Gerty and Urse.[1] These authors had observed that schizophrenic patients showed a decreased tolerance to intravenously administered dextrose, and therefore they attempted to determine whether this phenomenon was due to inhibition of insulin. They followed the blood sugar response to 1 unit of insulin in fasting rabbits which were given blood of schizophrenic patients intraperitoneally one hour before the injection of insulin and compared it with the response to the same dose of insulin after injection of normal blood. It was found that the average degree of insulin hypoglycemia in the rabbits treated with blood of schizophrenic patients was less marked than that in the rabbits treated with blood of normal persons. From this they concluded that the blood of schizophrenic patients was characterized by the presence of an insulin-inhibiting factor, and it was assumed that this factor was of etiologic significance for at least one group of the schizophrenic symptom complex, the differential diagnosis of which could be made with the insulin inhibition test.

These observations if confirmed would be of great importance. They would permit one to establish the diagnosis of schizophrenia or of one group of the schizophrenic complex with the help of an objective biologic test and would affect deeply the conception of the etiologic mechanism of this disease. Furthermore, they would indicate that the blood of persons who themselves are not resistant to insulin can produce such resistance when injected into an experimental animal.

We have tried to repeat the experiments of the authors, but our results are not in agreement with theirs.

From the Department of Medicine and the Otho S. A. Sprague Institute of the University of Chicago.

1. Meduna, L. J.; Gerty, F. J., and Urse, V. G.: Biochemical Disturbances in Mental Disorders: I. Anti-Insulin Effect of Blood in Cases of Schizophrenia, Arch. Neurol. & Psychiat. **47**:38-52 (Jan.) 1942.

METHOD AND MATERIAL

We examined the blood of 25 schizophrenic patients, for all of whom the diagnosis had been established clinically either in the psychiatric department of the University of Chicago or in the Manteno State Hospital.[2] All the patients were seriously deranged. All types of schizophrenia, catatonic, hebephrenic and paranoid, were represented. The ages varied from 16 to 51 years. The duration of the disease ranged from a few weeks to (in 1 instance) thirty years. Some of the patients had had metrazol treatment, but these persons also exhibited classic features of schizophrenia.

Twenty members of the staff and students of the University of Chicago were used as control subjects.

We followed the procedure of Meduna and his co-workers with a few exceptions. The procedure is a modification of the method of de Wesselow and Griffiths,[3] the principle of which is that the blood and insulin are injected at different times and at different sites into the experimental animal. The rabbits used weighed 2,000 Gm. and were kept under constant laboratory conditions for several weeks before the experiments. They had fasted for twenty-four hours before the intraperitoneal injection of 20 cc. of blood from a fasting person. The fasting blood sugar of the rabbit was determined before the injection of blood, and one hour later 1 unit of crystalline insulin was given subcutaneously. The blood sugar was estimated by the Miller-Van Slyke micromethod,[3a] and determinations were made one-half, one, two and three hours after the injection of insulin. Estimates beyond the three hour period seemed unnecessary, since the insulin effect occurs within this period. Our procedure differed from that of Meduna in two major respects.

1. Oxalated blood was used instead of fresh whole blood. We felt justified in making this modification because our previous experiments on insulin-resistant patients with diabetes had shown that oxalate does not interfere with the insulin inhibiting power of blood, and because Meduna and his co-workers themselves have demonstrated that the use of fresh blood is not essential, since they obtained similar results with plasma. A decisive motive in our variation of the technic was the observation that fresh blood tends to clot very easily, even in the peritoneal cavity, and that it is not resorbed quantitatively.

2. We used each rabbit as its own control; Meduna, Gerty and Urse employed each rabbit only once (except in a few experiments which they did not include in their statistical report) because of their belief "that even one injection of insulin alters the reaction of the animal to this substance." There is, however, little experimental or clinical evidence for such an assumption.[4] On the other hand, the variation in insulin sensitivity in different animals is so great that certain control procedures are necessary in order to make comparable tests of insulin

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2. Dr. David Slight, of the University of Chicago, and Dr. W. H. Baer, of the Manteno State Hospital, cooperated in this study.

3. de Wesselow, O. L. V., and Griffiths, W. J.: On the Possible Rôle of the Anterior Pituitary in Human Diabetes, Lancet **1**:991-994 (May 2) 1936.

3a. Miller, B. F., and Van Slyke, D. D.: A Direct Microtitration Method for Blood Sugar, J. Biol. Chem. **114**:583-595 (July) 1936.

4. (*a*) Jensen, H. F.: Insulin, New York, Commonwealth Fund, Division of Publications, 1938, p. 82. (*b*) Hill, D. W., and Howitt, F. O.: Insulin: Its Production, Purification and Physiological Action, London, Hutchinson & Co., Ltd., 1936.

sensitivity or insensitivity in different animals. Duplicate experiments and the "cross-over" method, or the use of each animal as its own control, are the most suitable of these procedures and are employed by the Insulin Committee of Toronto for the assay of insulin.[4a] The latter is carried out in the following way:

One half of a series of rabbits (100, or even more, animals) are given a dose of standard insulin, and the other half receive simultaneously a dose of the substance of unknown potency. About a week later the groups are "crossed over" and used for injections of the same substances. From the relation between the lowering of blood sugar produced by the standard insulin solution and that by the insulin solution of unknown strength, the activity can be calculated. The same procedure can be employed for the assay of insulin-inhibiting substances. The cross-over method alone can be used even here, when not enough material is available to perform a sufficient number of duplicate experiments. We tested, therefore, in the same animal the effect of physiologic solution of sodium chloride and insulin, then the effect of normal blood and insulin and, in a third experiment, the effect of the blood of schizophrenic patients and insulin. These three tests were done at intervals of seven days or more. The order of the three tests was varied in such a way that in some animals insulin and saline solution was given first, and in others normal blood or blood from schizophrenic patients. If possible we used further controls. In several instances we tested the same blood in different animals at the same time and in the same animal at different times.

In all experiments the percentage lowering of the blood sugar was calculated, and the values and curves thus obtained were compared for each animal individually. Also, average values and curves were computed from the results of the test with each kind of blood. Most importance, however, was given to the outcome of the individual tests in one and the same animal.

RESULTS

Our results are given in the table, which shows the percentage of loss of blood sugar in each animal after injection, respectively, of normal blood and insulin, of blood of schizophrenic patients and insulin and of saline solution and insulin. In the three vertical columns are given the results of the three types of injections in different animals, and the bottom line gives the average values for each kind of injection at the intervals at which they were determined. The horizontal lines show the results of the three tests in the same animal. In several instances the results of two tests with blood of schizophrenic patients are indicated; these are not duplicates but determinations with blood from two different patients. Results of duplicate experiments are not included in this table.

It is evident that the spread of values among different animals (vertical columns) is much greater than that between the different tests on the same animal, though the values for the test with saline solution and insulin are generally considerably lower than the other values.

A characteristic difference between the three groups is that 5 animals in the group receiving insulin and saline solution went into deep hypoglycemic coma between the first and the third hour, so that dextrose

had to be given and the experiments terminated, whereas in all but 1 of the animals of the two other groups the blood sugar curve could be followed through the three hour period. This observation seems to indicate that blood (normal blood, as well as that of schizophrenic

Experimental Data on Anti-Insulin Effect of Blood of Normal and Schizophrenic Persons *

	Percentage of Loss of Blood Sugar After Injection of 1 Unit of Insulin and											
	Physiologic Solution of Sodium Chloride				Blood of Normal Persons				Blood of Schizophrenic Patients			
Time after injection (Hr.) Animal No.	½	1	2	3	½	1	2	3	½	1	2	3
20	27	35	45	37	15	24	40	29	20	32	38	30
30	32	41	50	43	28	40	52	40	22	35	46	34
33	24	45	60	54	20	38	60	52	9	19	31	25
40	31	44	52	46	30	35	44	41	28	36	48	31
									31	39	40	33
49	29	48	64	46	19	27	36	29	29	40	55	34
50	36	60	65	+	35	49	62	48	39	53	67	53
51	23	42	53	41	27	32	58	35	25	35	54	30
									23	38	51	25
53	49	69	+	+	41	55	40	33	46	60	49	40
54	30	46	51	45	24	29	48	34	21	35	45	25
55	25	49	46	37	19	35	46	23	20	43	42	24
56	35	53	71	+	34	48	56	44	30	51	49	35
60	34	56	62	42	38	53	70	+	16	32	30	19
									32	54	68	55
61	28	41	55	31	25	29	41	18	15	18	20	13
64	32	43	52	38	27	39	35	22	30	46	42	25
									24	38	36	30
65	36	49	46	33	30	42	45	25	33	51	50	29
									29	46	42	28
70	26	50	65	+	20	48	58	32	21	52	50	35
74	41	+	+	+	39	65	42	28	36	63	48	30
77	33	51	59	41	26	45	53	36	22	40	48	33
86	28	43	53	45	32	47	53	30	28	46	55	32
89	37	46	44	30	25	28	24	11	30	43	40	25
Means	31.8	47.9	55.1	40.2	27.7	40.4	48.1	32.1	26.3	41.8	45.7	30.8

* The three vertical columns show the results of the three treatments in different rabbits; the results of the three tests in the same animal are represened in the horizontal lines. Significant differences between the effect of normal and that of schizophrenic blood in the same animal are indicated by underlining. The mean values for each kind of treatment are given in the line at the bottom. In the table, + indicates that the animal went into hypoglycemic shock and dextrose had to be given and the experiment terminated.

In several instances (animals 40, 51, 60, 64 and 65) two tests with blood from schizophrenic patients are indicated. These are not duplicates but tests with blood from different patients. Duplicate experiments are not included in this table.

patients) in the given amount of 20 cc. protected the rabbits to a certain degree against the full insulin effect.

The average loss of blood sugar in our experiments with insulin and saline solution was 55.1 per cent and was reached in two hours.

This proves that our animals had normal insulin sensitivity, for, according to definition, 1 unit is that amount of insulin which in a fasting rabbit weighing 2,000 Gm. will lower the blood sugar to about 45 mg. per hundred cubic centimeters.[4a] The average loss for our two groups treated with blood and insulin, was 48.1 and 45.7 mg., respectively, per hundred cubic centimeters. This indicates that insulin exerted a significant effect. The difference of less than 10 per cent between the tests with insulin and saline solution and those with blood and insulin is too small to be attributable to a specific anti-insulin factor in the blood, or even to be described as pronounced insulin inhibition.

If one compares now the two groups given, respectively, injections of blood of normal and of schizophrenic persons, one finds several variations.

Three samples of blood from schizophrenic patients inhibited insulin to a greater degree than did normal blood in the same rabbit. We accepted as significant a difference of 10 per cent or more. A difference of less than 10 per cent was disregarded because of the standard deviation for the method of estimating blood sugar and because of the variability of biologic tests. Thus, of 25 schizophrenic patients, 3, or 12 per cent, yielded a positive and 22, or 88 per cent, a negative result. Furthermore, 2 samples of normal blood inhibited insulin to a greater degree than did the blood of schizophrenic patients in the same animal. Thus, of 20 normal persons, 2, or 10 per cent, yielded a positive and 18, or 90 per cent, a negative result. These "positive" values are underlined in the table.

Six series of duplicate experiments with the same blood in different animals at the same time and 5 control experiments with the same blood in the same animal at different times showed, again, variations between different animals as high as those indicated in the table, whereas the variations in the same animal were small, indicating that the individual insulin sensitivity rather than the kind of blood determined the insulin hypoglycemia. Of special importance were the control tests with the blood of the 2 normal persons and the blood of the 3 schizophrenic patients in which pronounced insulin inhibition had been found. In the case of 1 schizophrenic patient, 5 tests were done within a period of three weeks, three of them in the same test animal and two as duplicates in different animals. Only once in this series could insulin inhibition be demonstrated a second time. Marble and associates [5] reported a similar observation, namely, that they were unable to reproduce their result with the blood of an insulin-resistant diabetic patient in whom at first

5. Marble, A.; Fernald, A. T., and Smith, R. M.: Effect of Human Diabetic Plasma upon Blood Sugar Curves in Rabbits Following Insulin, Endocrinology **26**:735 (May) 1940.

the rabbit test had indicated pronounced insulin inhibition. In 1 of the other 2 patients with schizophrenia the second test gave the same positive result as the first, and in the other patient the second test gave a negative result. Clinically, none of the 3 patients had diabetes. In 1 of the 2 normal persons the blood showed in a second experiment the same degree of inhibition as in the first, and in the second subject the result was negative.

Conclusion.—Treatment with blood (20 cc.) generally will moderate slightly the insulin hypoglycemia in rabbits. In a few instances mild insulin inhibition was observed, but this result was not constant with the blood of the same person, and it was observed with the blood of normal persons as well as with the blood of schizophrenic patients. Our experiments, therefore, did not give evidence of the presence of a specific insulin-inhibiting factor in the blood of schizophrenic patients.

COMMENT

In discussing inhibition of insulin by blood a distinction should be made between inhibition in vivo and that in vitro. It seems to be a physiologic quality of blood to inhibit or inactivate insulin in vitro. This phenomenon is best demonstrated with the method of Karelitz, Cohen and Leader.[6] These authors mixed insulin and blood in a test tube and injected the mixture into rabbits. The hypoglycemia so produced was less severe than that produced by a mixture of insulin and saline solution. This observation has been confirmed by several workers,[7] and though the mechanism of the process is not completely clear, it is believed that the enzymes of the blood, particularly of the white blood cells, inactivate the insulin.[8] Attempts to demonstrate an inhibiting effect of blood on insulin in vivo by injecting the two substances separately into animals (de Wesselow and Griffiths [3]) have been less regularly successful.[9] The blood of normal or of diabetic persons in the amounts generally employed (10 cc.) affects the insulin hypo-

6. Karelitz, S.; Cohen, P., and Leader, S. O.: Insulin Inactivation by Human Blood Cells and Plasma in Vitro, Arch. Int. Med. **45**:690 (May) 1930.

7. Rosenthal, F.; Friedheim, J., and Nagel, R.: Ueber die Insulin zerstörende Kraft der Erythrocyten, Klin. Wchnschr. **13**:1121 (Aug. 4) 1934. Bürger, M., and Kohl, H.: Inaktivierung des Insulins durch Blut, Arch. f. exper. Path. u. Pharmakol. **174**:130, 1933. Mauriac, P., and Aubertin, E.: Sur le pouvoir de neutralisation du sang de sujets diabétiques et non diabétiques vis à vis de l'insuline, Compt. rend. Soc. de biol. **98**:233, 1928.

8. Rosenthal, F., and Behrend, R.: Zur Frage des fermentativen Mechanismus der Insulinresistenz, Ztschr. f. exper. Med. **53**:562, 1926.

9. (*a*) Rushton, J. S.: The Anti-Insulin Effect of Blood Plasma from Certain Diabetic Patients, Proc. Staff Meet., Mayo Clin. **15**:417 (July 3) 1940. (*b*) Dohan, F. C.: Analysis of Insulin Response of Rabbits After Injection of Diabetic Serum, Proc. Soc. Exper. Biol. & Med. **39**:24 (Oct.) 1938. (*c*) Marble and associates.[5]

glycemia little or not at all. Since, however, the degree of inhibition in vitro is roughly proportional to the amount of blood used, it is likely that in in vivo experiments, also, larger amounts of blood might produce a measurable inhibiting effect. The slight moderation of the insulin effect observed in our experiments with the blood both of normal and of schizophrenic persons seems to suggest this. Even so, insulin inhibition or complete inactivation has been observed in in vivo experiments only with blood of insulin-resistant patients, and mostly with the blood of insulin-resistant diabetic patients with pituitary involvement, particularly acromegaly.[10] It has been assumed that this type of insulin inhibition is caused by a pituitary factor present in the blood of the patient. Dohan's [9b] experiments on the inhibition of insulin hypoglycemia by extracts of the anterior lobe of the pituitary give support to this theory. However, not all diabetic patients who are insulin resistant and not all diabetic patients with involvement of the pituitary show this phenomenon. It can only be stated that in those instances in which marked insulin inhibition by blood could be demonstrated in vivo, the blood was taken from an insulin-resistant or insulin-insensitive patient. Though a high degree of insulin inhibition is not necessarily a quality of the blood of insulin-resistant patients, it does not seem to occur without clinical resistance to insulin.

Knowledge of insulin resistance has until recently been limited to its rare occurrence in diabetes, in which it may be primary or "idiopathic" but usually develops secondarily during the course of treatment with insulin. The rarity of this secondary resistance to insulin suggests that it is not directly the result of the insulin treatment itself.

With the advent of the insulin shock treatment of schizophrenia, more information on this subject has become available, and it is certain that insulin resistance in this disease is also rare indeed. Whereas about 50 cases of insulin resistance in diabetic patients have been reported,[10a] only a few instances have been found during the shock treatment of schizophrenic patients. In a statistical study of 6,587 insulin shock treatments, no mention is made of a case in which insulin failed to produce shock or in which unusually large doses had to be given.[11] In the few instances which have been reported elsewhere the patients were insulin sensitive when the treatment was started or when the diagnosis was made and became resistant during the treatment.[12] Such was the

10. (*a*) Martin, W. P.; Martin, H. E.; Lyster, R. W., and Strouse, S.: Insulin Resistance, J. Clin. Endocrinol. **1**:387 (May) 1941. (*b*) Marble, A.: Insulin Resistance: Report of Marked Insensitiveness of Long Duration Without Demonstrable Cause, Arch. Int. Med. **62**:432 (Sept.) 1938. (*c*) Marble and associates.[5]

11. Frostig, J. P.: Clinical Observations in the Insulin Treatment of Schizophrenia, Am. J. Psychiat. **96**:1167 (March) 1940.

12. Tillim, S. J.: Observations of Insulin Sensitivity, Am. J. Psychiat. **96**:361 (Sept.) 1939. Reese, H. H., and Vander Veer, A.: Experiences with Insulin Shock Therapy of Schizophrenia, Arch. Neurol. & Psychiat. **59**:702 (April) 1938.

situation in the Toronto case,[13] to which Meduna referred. The patient, though eventually requiring 1,000 units to produce coma, went into hypoglycemic shock after only 40 units at the beginning of his treatment. This indicates that there was little relation between the patient's schizophrenia and his insulin resistance.

Thus, our negative laboratory results find confirmation in clinical facts. The lack of insulin insensitivity or insulin resistance in patients with schizophrenia has its parallel in the lack of any decided insulin-inhibiting power of the blood of schizophrenic patients as tested in animals. In the few instances in which an anti-insulin factor could be demonstrated in the blood of schizophrenic patients, there was no reason to assume a causal relation between the schizophrenia and the insulin inhibition.

It is necessary at this point to consider in some detail the experiments of Meduna, Gerty and Urse. Their conclusions are in the main based on the average loss of blood sugar in each of two series of experiments. In the first series, with 20 rabbits, they studied the hypoglycemia produced by injection of normal blood followed by insulin, while in the second series (with 51 rabbits) the blood of schizophrenic patients was substituted for normal blood in experiments of the same type. Since each rabbit was used only once, not only the kind of blood which was injected but the test animals were different in the two series. Also, each subject's blood was examined only once, and no duplicate experiments were performed. As in our own experiments, a pronounced insulin effect was obtained in both series of animals. The greatest loss of blood sugar in the series treated with normal blood averaged 65.7 per cent, and that in the series treated with blood from schizophrenic patients, 52.8 per cent. The difference of 12.9 per cent was found to be statistically significant. Aside from the fact that we have been unable to confirm this difference, there are certain features of the experiments under discussion which we regard as open to criticism:

There was a wide variation between comparable values for blood sugar in the individual animals of both the group treated with normal blood and the group treated with blood from schizophrenic patients. For example, the loss of blood sugar for the one hour period in the first group ranged from 38 to 63 per cent, and that in the second group, from 15 to 68 per cent. Such variations, interpreted by Meduna to indicate differences in the insulin-inhibiting power in the different specimens of blood, could just as well be taken to show various degrees

13. Banting, F. G.; Franks, W. R., and Gairns, S.: Anti-Insulin Activity of Serum of Insulin Treated Patient, in Hall, S. E.: Physiological Studies in Experimental Insulin and Metrazol Shock, Am. J. Psychiat. **95**:562 (Nov.) 1938.

of insulin sensitivity in the test animals. As a matter of fact, similar variations are observed in rabbits which receive insulin alone and are not treated with blood at all. It was this experience which led to the institution of the cross-over method and the use of large numbers of duplicate experiments for the assay of insulin. It would be necessary to exclude the possibility of variation in insulin sensitivity by means of these control methods before accepting the conclusion of Meduna and his associates as valid. Such controls were performed by these investigators in only a few instances, only 1 of which was detailed in their paper, and the results were not included in the statistical evaluation of the data.

Since proof is lacking that the wide individual variations in the loss of blood sugar really represent differences in the insulin-inhibiting power of the different specimens of blood, it is impossible to accept the recommendation of Meduna and his associates that this procedure be used as a test for schizophrenia. Indeed, Kraines [14] reported that he found in similar investigations not only extreme variations from person to person but different results with the blood of the same patient examined from day to day, and he stated that "it is impossible to use the test diagnostically for any patient."

SUMMARY

Experiments on the insulin-inhibiting power of blood of normal and of schizophrenic patients are reported. The relation between insulin inhibition by blood and clinical insulin resistance is discussed. No indication of the presence of an anti-insulin factor in the blood of schizophrenic patients could be found.

950 East Fifty-Ninth Street.

14. Kraines, S. H., in discussion on Meduna, L. J.; Gerty, F. J., and Urse, V. G.: Biochemical Disturbances Associated with Mental Disorders: I. The Anti-Insulin Effect of the Blood in Schizophrenia, Arch. Neurol. & Psychiat. **46**:192 (July) 1941.

THE PYRAMIDAL TRACT

A STUDY OF RETROGRADE DEGENERATION IN THE MONKEY

A. M. LASSEK, M.D., PH.D.
CHARLESTON, S. C.

Since Nissl [1] published his original article, the retrograde method has been widely employed in searching for the cells of origin of both central and peripheral neurons. On the basis of results obtained with this procedure, it is assumed that the power of withstanding axon injury is less in central than in peripheral neurons.[2] The view that the so-called Betz cells of area 4 (motor cortex) give sole origin to the fibers of the pyramidal tract is based largely on the results of the retrograde approach, especially the study of Holmes and May.[3] These investigators, as well as numerous others,[4] unanimously reported the eventual breakdown and disappearance (atrophy) of the so-called giant cells of area 4 in several species of mammals following injury to the pyramidal fibers. As a corollary, neurons throughout the pyramidal tract should concomitantly vanish, with loss of giant cells. In disharmony with these observations on cellular changes are those of other workers,[5]

From the Department of Anatomy, Medical College of the State of South Carolina.

This work was aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Nissl, F.: Ueber eine neue Untersuchungsmethode des Centralorgans speciell zur Feststellung der Localisation der Nervenzellen, Centralbl. f. Nervenh. u. Psychiat. **5**:337-344, 1894.

2. Polyak, S. L.: The Retina, Chicago, University of Chicago Press, 1941.

3. Holmes, G., and May, W. P.: On the Exact Origin of the Pyramidal Tract in Man and Other Mammals, Brain **32**:1-43, 1909.

4. (*a*) Ballet, G., and Faure, M.: Atrophie des grandes cellules pyramidales dans la zone motrice de l'écorce cérébral après la section expérimentale des fibres de projection chez le chien, Rev. neurol. **7**:426, 1899. (*b*) von Gudden: Ueber die Frage der Localisation der Functionen der Grosshirnrinde, Allg. Ztschr. f. Psychiat. **42**:478-499, 1886. (*c*) Levin, P. M., and Bradford, F. K.: The Exact Origin of the Corticospinal Tract in the Monkey, J. Comp. Neurol. **68**:411-422, 1938. (*d*) Marinesco, G.: Sur les altérations des grandes cellules pyramidales consécutives aux lésions de la capsule interne, Rev. neurol. **7**:426, 1899. (*e*) Schröder, P.: Die vordere Zentralwindung bei Läsionen der Pyramidenbahn und bei amyotrophischer Lateralsklerose, Monatschr. f. Psychiat. u. Neurol. **35**:1-25, 1914.

5. (*a*) Davison, C.: Syndrome of the Anterior Spinal Artery of the Medulla, Arch. Neurol. & Psychiat. **37**:91-107 (Jan.) 1937. (*b*) Dercum, F. X., and Spiller,

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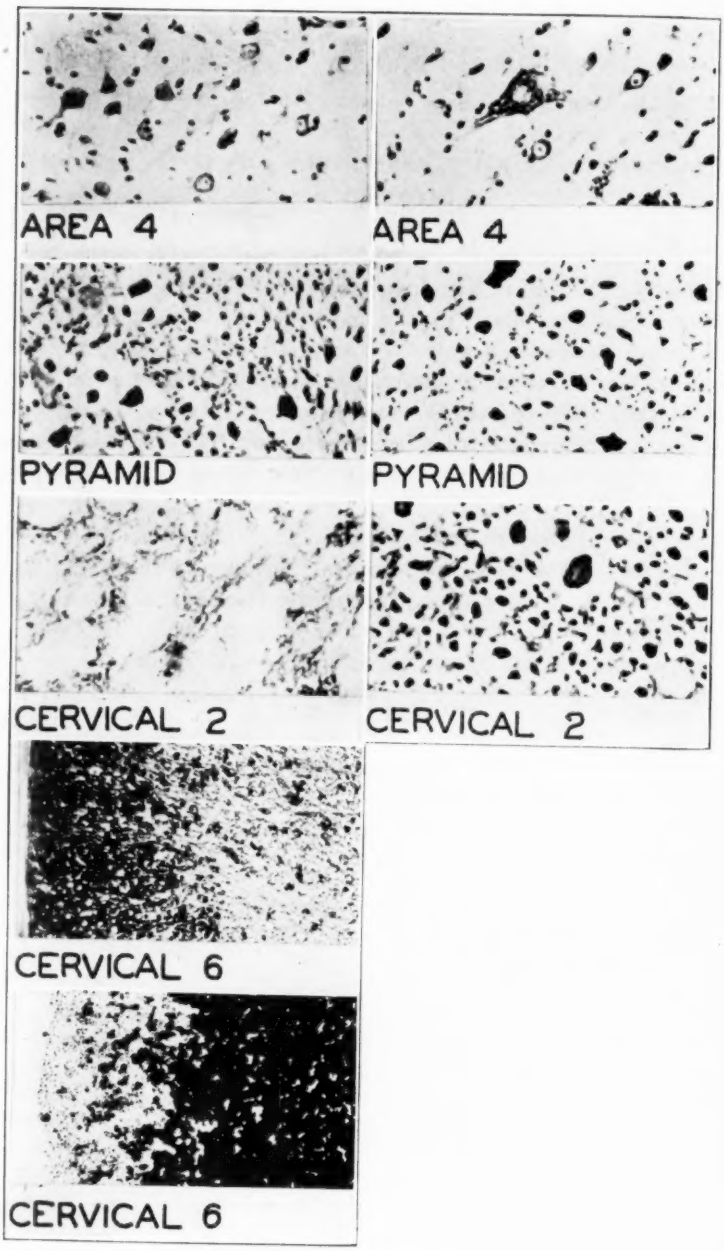

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who have noted that pyramidal fibers remain intact and apparently normal in the lower portion of the brain stem long after their continuity is interrupted below.

These divergent observations on the cell and fiber changes in the pyramidal system are confusing and incompatible with current conceptions of central neurons. It is the purpose of the present investigation to make a correlative study of the rostral and distal effects of section of the pyramidal tract in the monkey.

MATERIAL AND METHODS

Hemisection of the spinal cord was made at the first cervical level in 3 monkeys (Macacus mulatta). The operative approach was in the usual manner through the atlanto-occipital membrane. The animals were killed at intervals of one, three and ten months. Sections 10 microns in thickness taken 500 microns apart through the motor cortex of both sides were stained by the cresyl violet technic. Five micron sections (paraffin) through representative parts of the mesencephalon, pons, medulla and four regions of the spinal cord were stained by several standard silver methods. The area and extent of the hemisections were

W. G.: A Case of Syringomyelia Limited to One Posterior Horn in the Cervical Region, with Arthropathy of the Shoulder-Joint and Ascending Degeneration in the Pyramidal Tracts, Am. J. M. Sc. **112**:683-685, 1896. (*c*) Hunt, J. R.: The Retrograde Atrophy of the Pyramidal Tract, J. Nerv. & Ment. Dis. **31**:504-512, 1904. (*d*) Kernohan, J. W., and Woltman, H. W.: Incisura of the Crus Due to Contralateral Brain Tumor, Arch. Neurol. & Psychiat. **21**:274-287 (Feb.) 1929. (*e*) Spiller, W. G.: A Microscopical Study of the Spinal Cord in Two Cases of Pott's Disease, Bull. Johns Hopkins Hosp. **19**:125-133, 1898. (*f*) Spiller, W. G.: A Case of Primary Degeneration of the Pyramidal Tracts, J. Nerv. & Ment. Dis. **29**:265-274, 1902. (*g*) Tower, S. S.: Pyramidal Lesion in the Monkey, Brain **63**:36-90, 1940. (*h*) Wechsler, I. S.; Brock, S., and Weil, A.: Amyotrophic Lateral Sclerosis with Objective and Subjective (Neuritic) Sensory Disturbances, Arch. Neurol. & Psychiat. **21**:299-310 (Feb.) 1929. (*i*) Williamson, R. T.: The Direct Pyramidal Tract of the Spinal Cord, Brit. M. J. **1**:946-947, 1893.

EXPLANATION OF FIGURE

Unretouched photomicrographs of parts of the pyramidal system of the monkey taken ten months after hemisection at the level of the first cervical segment on the left side.

Left side: lowest section (sixth cervical segment), Marchi stain, showing degeneration of the pyramidal tract, × 90; next above (sixth cervical segment), osmic acid stain, showing degeneration of the pyramidal tract and preservation of the ascending myelinated fibers lateral to it, × 90; next (through center of pyramidal tract at the second cervical level), protein silver (protargol) stain, showing complete loss of pyramidal tract fibers, × 770; next, protargol stain, showing preservation of fibers of the affected pyramidal tract, × 770; top (area 4 of affected side), cresyl violet stain, × 160.

Right (normal) side: lowest (pyramidal tract at the second cervical level), protargol stain, × 770; second, normal fibers in pyramid, × 770; top, normal area 4, cresyl violet stain, × 160.

determined by making sections through the lesion cut parallel to the long axis of the cord and staining some of them by Van Gieson's and others by Davenport's protein silver (protargol) method as a check for continuity. By this procedure the histologic picture of the giant cells in area 4 of both sides, the central end of the pyramidal neuron as far as the first cervical segment and, lastly, the distal portion of the neuron within the cord could be examined and correlated.

RESULTS

Checking of the lesions in the 3 specimens showed that the pyramidal tract was severed at the first cervical segment. The histologic picture of the pyramidal system (affected side) was nearly identical in the 3 monkeys. Area 4 was atypical; the pyramidal tract axons in the peduncles, the pons and the medulla appeared to be normal under the microscope, while distal to the injury the fibers had undergone secondary degeneration and disappeared.

On general examination of area 4, one gained the impression that the Betz, or giant, cells had vanished. Without knowing that the central axons were preserved in the brain stem, one might conclude that this was the case, as have all investigators using this method. I could see no concrete evidence of cellular disappearance, such as "ghost cells," partial atrophy or advanced gliosis. It is my belief that these huge cells had uniformly decreased in magnitude, primarily because of loss of Nissl or other substances, and that they had been affected by the axonal injury in such a way that they were incapable of readjustment. The Betz cells on the left, or unaffected, side appeared normal.

The most searching examination of sections of the brain stem with the various stains failed to reveal any anatomic differences between the upper portion of the axons of the pyramidal tract on the two sides. The histologic picture was normal from the mesencephalon to the first cervical segment. No spaces or degenerated axons in any stage of atrophy could be discerned as an indication of fiber loss. Counting of fibers with a Whipple square revealed no discrepancy in the number per unit area of the two halves.

Below the lesion, the lateral corticospinal fasciculus was degenerated, with complete loss of fibers. Only a few occasional scattered axons, belonging either to other systems or to the fasciculus proprius (ground bundle), were present.

These results do not appear to be characteristic of the pyramidal tract alone, for in all 3 animals extensive retrograde degeneration with disappearance of axons did not occur in the ascending tracts below or in the descending tracts above the lesion.

COMMENT

The results obtained agree with the reports of those investigators [4] who have found that the pyramidal tract fibers do not undergo retro-

grade degeneration (implying breakdown and disappearance) when the bundle is severed below. In this experiment the longest time allowed was ten months. Davison [5a] made his observation after twenty-three months on the human brain (case 2); Tower,[5g] after thirty-two months on the monkey brain, and Spiller,[5f] after five years, and Schröder [4o] (case 1) after twenty years, on the human brain. The central ends of pyramidal fibers appear, therefore, to maintain their integrity for many years after severance of their axons.

I assume, on the basis of my observations, that the cells of origin of the pyramidal tract fibers remain in a state capable of maintaining the anatomic integrity of the upper part of the axis-cylinders. With respect to the so-called Betz, or giant, cells the picture was difficult to interpret. They seemed to have disappeared, as described by all investigators using this approach. No typical giant cells were seen in the fifth layer of area 4. I believe these cells had shrunken, as a result primarily of the loss of Nissl or other substances, so that it was difficult to differentiate them from the smaller pyramidal cells of this area. This occurred as early as twenty-eight days in the monkey. Levin and Bradford,[4c] in their investigation on chromatolytic changes, stated that 1 of their monkeys "was permitted to survive 28 days, an interval which proved excessive, most of the degenerating cells having already disappeared." Their hemisection was made at the fourth cervical segment.

The upper part of the neuron must also remain physiologically active; otherwise it would atrophy from disuse. Tower [5g] gave the explanation that collaterals of pyramidal axons to the pontile nucleus may be sufficient to keep the fibers anatomically and functionally intact. Another interpretation is that impulses coming into the cell body may be sufficient to maintain the integrity of the neuron. In cutting the central branches of the dorsal roots, for instance, no reaction occurs in ganglion cells, but severing the peripheral branches which carry impulses to the same cells produces typical chromatolytic and atrophic changes.[6]

The question arises whether the pyramidal tract is unique in being the only bundle in the central nervous system which fails to undergo retrograde degeneration when its axons are severed. If the presence of collaterals is the explanation, then breakdown and disappearance of the central end of axons should be rare, for it is probable that most fibers in the central nervous system give off side branches, whether they are ascending or descending. The same should be true if the presence of incoming stimuli into the cell body is the vital factor in maintenance of the neuron. In the 3 specimens studied in this investigation, no retro-

6. Hare, W. K., and Hinsey, J. C.: Reactions of Dorsal Ganglion Cells to Section of Peripheral and Central Processes, J. Comp. Neurol. **73**:489-502, 1940.

grade degeneration was noted in the ascending tracts below or in the descending tracts above the lesion. I have examined the literature in an attempt to find an explanation for this, but the only conclusion I can draw at present is that investigators utilizing this method have concentrated on the changes occurring within the cells rather than in the whole neuron.

The results of this investigation may be against the view that the Nissl substance is concerned completely with the nutrition of the nerve fiber. In this experiment, chronic chromatolysis was produced in the so-called giant cells of area 4, without noticeable changes in the axis-cylinders of the pyramids of the mature monkey. The exact role of the Nissl substance has been an enigma for the past fifty years or more. Its only consistent characteristic apparently is that it is extremely unstable and sensitive to influences of all kinds. Geist [7] stated that chromatolytic changes in efferent nerve cells are dependent on at least four factors: (1) the species and age of the animal; (2) the distance of the injury from the cell body; (3) the interval between the injury and the staining of the tissue, and (4) the histologic and functional type of neuron. A wide variety of conditions are known to produce loss of tigroid material. It occurs chronically in senile involution. Acute changes have been reported to have been produced by elevation of temperature, cold, deprivation of water or food, insomnia, anemia, poisons and electric shock. Long ago it was recognized that many neurologic diseases cause chromatolysis, as well as various non-nervous conditions.[8] It is also admitted by the majority of investigators using the retrograde approach that the method does not work satisfactorily with small neurons. This is due to the fact that diminutive nerve cells contain little Nissl substance, the nucleus normally may be eccentrically placed in the cytoplasm and, finally, when the axon is injured it is supposed to dissolve without leaving any evidence of its existence. Since there is no other pathway in the spinal cord which contains as many minute fibers as the corticospinal tract, the retrograde method would probably be highly ineffective with this system. These facts indicate that one must be cautious in interpreting results obtained by the chromatolytic approach.

All of the observations reported for the monkey have been confirmed in the cat and rat. It appears, therefore, that retrograde degeneration with breakdown and loss of nerve fibers does not occur in the pyramidal system of mammals. The question is raised whether it occurs in any of the long descending or ascending tracts of the brain

7. Geist, F. D.: Chromatolysis of Efferent Neurons, Arch. Neurol. & Psychiat. **29**:88-103 (Jan.) 1933.

8. Robertson, W. F.: Normal and Pathological Histology of the Nerve Cell, Brain **22**:289-291, 1899.

stem or the spinal cord. The axons within the central nervous system may be just as resistant to injury as those of the peripheral nervous system.

CONCLUSIONS

Retrograde degeneration with breakdown and loss of neurons does not occur in the pyramidal system of the monkey after section of the pyramidal fibers. Changes occur in the so-called Betz, or giant, cells of area 4, characterized by shrinkage and loss of Nissl substance, so that the normal configuration of these cells is lost. The Nissl substance may not be concerned with the nutrition and metabolism of the axon. I believe the retrograde method fails to prove that the so-called Betz, or giant, cells give sole origin to the pyramidal tract fibers. The question is raised whether retrograde degeneration with dissolution of axis-cylinders can be produced in the spinal cord and brain stem of the central nervous system.

INTELLIGENCE IN CEREBRAL DEFICIT STATES AND SCHIZOPHRENIA MEASURED BY KOHS BLOCK TEST

THEODORE LIDZ, M.D.*

JAMES R. GAY, M.D.

AND

CHRISTOPHER TIETZE, M.D.*

BALTIMORE

A means of ascertaining the presence of deterioration and a reliable method for measuring the intellectual capacities of persons suffering from deficits resultant on structural damage to the brain are much needed tools for the neurologist and the psychiatrist. The measurement of the intelligence of deteriorated persons presents difficulties not encountered in the measurement of intelligence of persons with undamaged brains. Lack of clarity concerning the problems involved, together with the unwarranted grouping of histogenic deteriorations and schizophrenic dilapidations in a single category has resulted in the construction of procedures which are not reliable and are rarely practicable.

Many intelligence tests measure what the subject has been capable of learning by means of his intelligence rather than the actual capacity for active mentation at the moment. Such methods are reliable when one is testing native endowment. Patients suffering from cerebral damage, however, may no longer possess the mental abilities by means of which learning had been accumulated. The information may remain after the intellect by which it had been gathered has deteriorated. Information, social forms, habitual modes of behavior and even well ingrained methods of thinking may be retained, forming a mask which

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From the Henry Phipps Psychiatric Clinic.

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hides the true status. Procedures intended for the measurement of the intelligence of the deteriorated patient must be concerned with the capacity for active mentation at the moment and be free from the influence of material acquired by the patient's former endowment.

A procedure intended to ascertain the level of intelligence which the patient possessed prior to the cerebral damage must fulfil the opposite requirements. The capacity for active mentation should not be tested, for it may be impaired. Assets which require intelligence to attain and which remain after the intelligence is diminished are sought. Necessarily, this will be static material which has become thoroughly ingrained and can be given by the patient without reflection. The requirements are difficult to satisfy and must be taken to represent an ideal goal. It has been found that, despite educational handicaps or foreign birth, a person's vocabulary is an excellent measure of his intelligence, for he acquires the tools necessary to express his ideas.[1] The vocabulary becomes well ingrained and, as first pointed out by Babcock,[2] is among the assets best retained after deterioration. Unfortunately, vocabulary is tested by definition, which requires some degree of reflection at times, and, as noted by Simmins,[3] the vocabulary also deteriorates. Although the vocabulary test appears to be the best measure of what the intelligence of the deteriorated patient has been, it can be utilized only guardedly. Still, when the vocabulary has deteriorated appreciably, the intellectual impairment is sufficiently advanced to be apparent without special examination.

The Shipley-Hartford scale,[4] although constructed on a different premise, fills the requirement of contrasting the score on tests which require active mentation with the score on a test of vocabulary knowledge. Its construction as a test which is to be self administered greatly reduces its reliability and range of usefulness in work with psychotic patients. It has further limitations. The difficulty in formulating tasks free from the influence of past learning was noted by Vigotsky,[5] when he indicated that verbal tests for concept formation are not satisfactory because words are the carriers of concepts which

1. Wechsler, D.: The Measurement of Intelligence, Baltimore, Williams & Wilkins Company, 1939.

2. Babcock, H.: An Experiment in the Measurement of Mental Deterioration, Arch. Psychol., 1930, no. 117.

3. Simmins, C.: The Measurement of Mental Deterioration, Brit. J. M. Psychol. **14**:113, 1934.

4. Shipley, W. C.: A Self-Administering Scale for the Measuring of Intellectual Impairment and Deterioration, J. Psychol. **9**:371, 1940. Shipley, W. C., and Burlingame, C. C.: A Convenient Self-Administering Scale for Measuring Intellectual Impairment in Psychotics, Am. J. Psychiat. **97**:1313, 1941.

5. Vigotsky, cited by Kasanin, J., and Hanfmann, E.: An Experimental Study in Concept Formation in Schizophrenia, Am. J. Psychiat. **95**:35, 1938.

are already organized prior to the onset of illness. The procedure utilized to measure the intelligence of the deteriorated patient should be a performance test which does not depend on previous learning for solution. The various methods which have been found suitable for the qualitative study of deficits in mentation are found to require the completion of unfamiliar tasks which demand from the subject some of the following attributes: plasticity to shift from one approach to another, selection from among a number of alternatives, analysis and synthesis and abstraction of common denominators.

The Kohs block test, originated as a performance test which requires analysis and synthesis,[6] has also been considered a test for abstraction [7] and a test requiring plastic shift in approach.[8] It also requires clear configurational perception and the selection of alternatives. There have been favorable reports on its use in the study of patients with cerebral lesions.[9] In the examination of such patients which we have carried out for various reasons, we have found that the Kohs test appears to give the best single indication of the patient's intellectual resources and furnishes a reliable guide for the planning of more detailed studies. It is singularly free from the influence of past experience.

As a test of the intelligence of deteriorated patients, the Kohs block test has a collection of other advantages not found in any other single procedure.

ADVANTAGES OF KOHS BLOCK TEST

1. *Reliability.*—Its reliability as a method of measuring the intelligence of normal subjects is attested to by the very high correlation with the Stanford-Binet test ($r = 0.84$), among the highest of all test correlations. Wechsler [1] found that the modification of the block test used in the Bellevue scale was the best single item, correlating more closely with the total score of the battery ($r = 0.73$) than any other single test, including the verbal tests. He found that it conformed to all the statistical standards for a good test and, "surprisingly," seemed

6. Kohs, S. C.: Intelligence Measurement, New York, The Macmillan Company, 1923.

7. Bolles, M., and Goldstein, K.: A Study of the Impairment of "Abstract Behavior," Psychiatric Quart. **12**:42, 1938.

8. Nadel, A.: A Qualitative Analysis of Behavior Following Cerebral Lesions, Arch. Psychol., 1938, no. 224.

9. Bolles and Goldstein.[7] Nadel.[8] Freeman, W. J., and Watts, J.: Psychosurgery, Springfield, Ill., Charles C. Thomas, Publisher, 1942. Benton, A. L., and Howell, I. L.: Use of Psychological Tests in Evaluation of Intellectual Function Following Head Injury: Report of Case of Post-Traumatic Personality Disorders, Psychosom. Med. **3**:138, 1941. Lidz, T.: Study of Effect of Right Frontal Lobectomy on Intelligence and Temperament, J. Neurol. & Psychiat. **2**:211, 1939.

to measure "the same sort of thing that verbal tests measure." A test which is among the most reliable means of measurement of intelligence in persons with undamaged brains can be expected to be more reliable than less well standardized procedures when applied to measuring the intelligence of deteriorated persons.

2. *Range.*—The test measures a wide range of intelligence, from a level where little, if any, reflective thinking is possible to superior levels. The gradations are discrete and well spaced.

3. *Use for Adults.*—Most performance tests, planned for children, are of little interest to adults. The block test is well accepted as a stimulating challenge.

4. *Retesting.*—Although the block test is not a paired test, it may be used several times without appreciable change in score. When the test is administered a second or a third time the designs are presented upside down or placed on a side. Each design is either red and white or blue and yellow. The same patterns can be presented in the opposite color scheme in retests.

5. *Qualitative Observation.*—The manipulations of the blocks by the subject in attempts to form the designs often permit pertinent observations concerning the thinking processes by means of which solution is achieved.

6. *Hemiplegic and Aphasic Patients.*—As the test can be performed with one hand, even the nondominant hand, hemiplegic patients can be tested. As it is a nonverbal test, which does not require the recognition of objects or the names of objects, it is useful in testing the intelligence of aphasic patients, who form a large class of patients suffering from cerebral deficits. In contrast to the opinion commonly held, performance tests require the use of symbolic processes, which for the most part concern language, but the elimination of actual verbalization decreases the confusion caused when the use of words is required of the aphasic patient.

7. *Time Factor.*—Utilization of speed of performance as a major factor in scoring, as in the Babcock test for deterioration,[10] diminishes the usefulness of a test, for patients with motor disabilities and schizophrenic and depressed patients may be penalized unduly. In the Kohs test speed is a factor, but not a decisive one. Few patients who can complete a design only when unlimited time is allowed can form the next design under any circumstances. It would be possible to restandardize the test and virtually to eliminate the time factor.

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10. Babcock, H.: Time and the Mind, Cambridge, Mass., Sci-Art Publishers, 1941.

8. *Simplicity.*—Special training is not required to administer the test accurately. A few trials suffice to familiarize the examiner with the procedure, and there is little room for subjective interpretation in scoring.

THE TEST PROCEDURE

In the study of the intelligence of patients which is to be described, the mental age obtained by means of the Kohs block test was considered the measure of the subject's intelligence at the time of testing. The mental age obtained by the use of the Stanford-Binet vocabulary score [11] was taken as the indication of the level of intelligence which the patient had formerly possessed. The complete Stanford-Binet test was given the patient to check against gross error and to record the intelligence as measured by the standard procedure, but this test does not enter into the method which is being outlined. The difference between the mental age on the vocabulary test and that on the Kohs test was considered as the measure of intellectual deterioration.

The method of administration of the Kohs block test may be found in Kohs's book,[6] but the procedure was modified in several respects. The technic will be briefly outlined so that the reader may follow the discussion more readily.

The test material consists of 16 identical 1 inch (2.5 cm.) "color cubes" and 17 standardized designs of graded complexity drawn on separate cards to a 1:4 scale. Each cube has four solidly colored sides, blue, red, white and yellow, a fifth side divided diagonally into red and white and a sixth side divided diagonally into blue and yellow. It is explained to the subject that the cubes are identical, and the various sides are pointed out. A simple sample design is presented, and he is requested to reproduce the pattern with the upper surface of the blocks. All 16 cubes are given him, and it is explained that, although only 4 are necessary for the sample design, more will be necessary for some patterns. The method of forming the sample pattern is illustrated when necessary. The subject is then requested to make the first design as rapidly as possible and is then offered one design after another until failure occurs on three consecutive patterns. If, when the tenth design, which requires 9 blocks, is reached, the patient does not realize that more than 4 blocks are needed, he should be told. The time permitted for the completion of each design is found on the design card, but the precise time is recorded, as bonus scores are given for rapid completion.

Kohs scored the test by taking both speed and the number of moves into consideration. Almost all workers have found the counting of moves arbitrary. Disregarding the number of moves simplifies the procedure and alters the score but little. As neglect of the number of moves raises the score, it appeared fully justified for the purpose to which the test was put, as will become apparent.

The scoring and calculations of the mental age were made according to the tables in Kohs's book.[6] A perfect performance is equivalent to a mental age

11. Terman, L. M.: The Measurement of Intelligence, Boston, Houghton Mifflin Company, 1916.

of 20 years, but, for the purpose of comparison with the vocabulary score, an upper limit of 18 years was arbitrarily established. The lower limit of 5 years 3 months was taken to indicate ability to complete the simplest design in unlimited time.

The total number of words defined adequately on the Stanford-Binet vocabulary test was expressed in terms of mental age by interpolating the score into the Binet scale; i. e., 20 words on both lists is equivalent to a mental age of 8 years, 25 words to a mental age of 9 years, 30 words to a mental age of 10 years, etc. In order to err on the side of not overestimating the former level of intelligence, the mental age of the subject was considered to be at the year level which had been passed successfully without addition of months; e. g., 23 words were scored as 8 years and not as 8 years and 7 months. For this reason the mental age on the vocabulary test should average 6 months higher than the figure actually given. This, together with the neglect of the number of moves on the Kohs test, adds significance to the calculations presented.

The assumption was made that patients who had not deteriorated would show little difference in the mental ages obtained by the three methods: the total Stanford-Binet, the vocabulary and the Kohs test. The correlations (r), according to Kohs,[6] are: Binet-Binet vocabulary test, 0.91; Binet-Kohs, 0.84; vocabulary-Kohs, 0.77. These correlations, however, were established by testing children. For proper evaluation it would be necessary not only to establish the correlations for adults, but, according to Wechsler,[1] establish them for adults at varying age levels. Despite lack of the essential statistical corroboration for the basic assumption, there is considerable evidence in its favor, such as the work of Wechsler on adults with a variant of the Kohs test and the results of the tests on schizophrenic patients, which will be given.

CLINICAL APPLICATION

All patients examined by the procedure are included in the material to be presented, with the exception of 6 who were either psychopathic personalities or suffered from depressive psychoses. None of these patients showed a lower mental age on the Kohs test than on the vocabulary test, but the group is too small to furnish an adequate control series. There were also a small number of severely deteriorated senile persons and patients with dementia paralytica who could not be tested, for they were incapable of attaining any score on the Kohs test; these subjects were all in the extreme stage of deterioration. The remaining patients fall into three general groups.

1. Patients with cerebral lesions:
   (*a*) Patients suffering from clinically appreciable intellectual deficits following various types of structural damage to the brain (21 patients; table 1).

(*b*) Patients with intellectual deficits to whom the vocabulary test could not be administered because of aphasic difficulties and who are therefore classified separately (5 patients; table 2).

TABLE 1.—*Measurement of Intelligence of Patients with Cerebral Deficit States*

Case No.	Age, Yr.	Education	Occupation	Diagnosis	Mental Age *			
					Binet	Vocabulary	Kohs	Vocabulary Minus Kohs
1(a)†	36	6th grade	Skilled laborer	Dementia paralytica	9-0	10	failed	....
(b)				After malaria therapy	9-4	12	6-6	5-6
(c)†				Social recovery	9-4	12	9-6	2-6
2	36	5th grade	Housewife	Dementia paralytica	8-2	8	5-3	2-9
3	?	4th grade	Mechanic	Dementia paralytica	10-6	10	6-3	3-9
4	34	College	Salesman	Dementia paralytica	12-0	14	7-0	7-0
5	27	High school	Housewife	Dementia paralytica	10-1	10	7-6	2-6
6	55	8th grade	Farmer	Dementia paralytica	10-8	10	7-8	2-4
7	24	High school	Stenographer	Dementia paralytica	12-11	14	8-2	5-10
8	41	8th grade	Mechanic	Dementia paralytica	10-8	14	9-8	4-4
9	50	High school	Executive	Dementia paralytica; social recovery	17-4	18	12-6	5-6
10	56	5th grade	Oysterman	Senile dementia	12-6	12	8-5	3-7
11	74	8th grade (?)	Tailor	Senile dementia (mild)	13-2	14	9-0	5-0
12	71	High school +	Attorney	Senile dementia (mild)	17-6	18	11-6	6-6
13†	39	Grades (?)	Laborer	Alcoholic deterioration	Unsatisfactory	14	5-3	8-9
14	56	College	Minister	Alcoholic deterioration	14-3	18	8-2	9-10
15	47	8th grade	Conductor	Alcoholism with Korsakoff's syndrome	16-6	16	9-6	6-6
16	40	High school (3 yr.)	Engineer	Alcoholic deterioration	16-3	18	12-5	5-7
17	34	College	Army officer	Alcoholism and trauma	17-0	16	13-2	2-10
18	50	5th grade	Mechanic	Alcoholism with Korsakoff's psychosis	11-0	9	10-5	—1-5
19	30	4th grade	Taxi driver	Carbon monoxide poisoning with Korsakoff's psychosis	12-6	13	12-11	0-1
20(a)†	36	College	Teacher	Carbon monoxide poisoning, severe	....	..	10-6	....
(b)					18-0	18	15-3	2-9
21	50	High school	Secretary	Softening of left frontal lobe	8-6	10	7-8	2-4

Biometric Constants

Binet mental age	m = 12.9 ± 0.5	S. D. = 3.2 ± 0.3
Vocabulary mental age	m = 13.6 ± 0.5	S. D. = 3.4 ± 0.4
Kohs mental age	m = 9.4 ± 0.4	S. D. = 2.7 ± 0.3
Difference between mental ages in vocabulary and in Kohs Test	m = 4.2 ± 0.4	S. D. = 2.6 ± 0.3

* In this table and the accompanying tables, mental age is expressed in years and months.
† Omitted from computation of biometric constants.

2. Patients concerning whom it was uncertain from the clinical evidence whether or not intellectual deficits were present (7 patients; table 3).
3. Patients with schizophrenia of various types, not including any who were out of contact or severely dilapidated (15 patients; table 4).

Patients with Cerebral Lesions.—The data on the 21 patients with cerebral lesions are assembled in table 1. The statistical calculations

exclude patient 13 because a satisfactory Binet score could not be obtained. The biometric constants for the 20 patients were as follows:

	Mean Mental Age	Standard Deviation
Binet	12.9 ± 0.5 years	3.2 ± 0.3 years
Vocabulary	13.6 ± 0.5 years	3.4 ± 0.4 years
Kohs	9.4 ± 0.4 years	2.7 ± 0.3 years

The mean difference between the mental age on the vocabulary test and the mental age on the Kohs test was 4.2 ± 0.4 years. The mean difference was thus over ten times its probable error, which

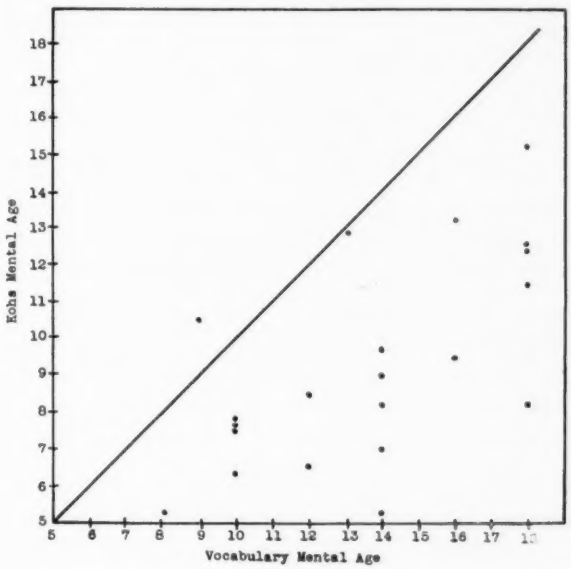

Chart 1.—Correlation of mental ages in the vocabulary and in the Kohs test in 21 cases of cerebral deficit.

indicates a very high degree of statistical significance. No significant difference would be expected for a series of normal persons.

Chart 1 shows the scatter of the individual cases when the Kohs mental age was plotted against the mental age on the vocabulary test. Cases of normal persons would be expected to scatter about the diagonal line drawn equidistant between the ordinate and the abscissa. For only 2 of the patients do the values not fall definitely below the line: 1 with the Kohs mental age 17 months higher than the vocabulary mental age and the other with the Kohs mental age only 1 month lower than the vocabulary mental age. These 2 patients, cases 18 and 19, suffered

from Korsakoff's psychosis and were the subjects of a paper by one of us [12] concerning the relatively intact mentation of certain patients with the Korsakoff psychosis when tested by methods which do not require recall or sequential performance. For all the remaining 19 patients the Kohs mental age was at least 2 years 4 months lower than the vocabulary mental age. For 13 patients there was a difference of at least 3 years, and for 10, a difference of more than 5 years.

Patients with Aphasia.—The Kohs block test offers a means of measuring the intelligence of aphasic patients that appears reliable as checked by other performance procedures and by scrutiny of their behavior. As the vocabulary test cannot be administered, there is no way of obtaining a quantitative comparison with the status of the intellect prior to cerebral damage.

TABLE 2.—*Measurement of Intelligence of Patients with Aphasia by the Kohs Block Test*

Case No.	Age, Yr.	Education	Occupation	Diagnosis	Kohs Mental Age
A1	49	Foreign	Chef	Subcortical motor aphasia	11-9
A2	63	High school	Male nurse	Amnestic aphasia	9-4
A3	60+	Grades (?)	Laborer	Receptive aphasia	9-3
A4	54	Grades (?)	Laborer	Severe amnestic aphasia	6-0
A5(a)	39	3d grade	Laborer	Severe aphasia following temporoparietal laceration	Failed
(b)				Improvement	7-6
(c)				Further improvement	9-0
(d)				Marked improvement 7 mo. after injury	11-0

The data on the 5 patients with aphasia are to be found in table 2. Not only does the Kohs score indicate the deterioration of mental capacities which had occurred in each patient, but the level of the score reflects the extent of the capacities which remained to each patient. The improvement in speech and comprehension shown by patient A5 over a period of seven months was paralleled by the rise in mental age. The most severely handicapped patient, A4, who could understand only the simplest commands and could utter but a few words, scored a mental age of but 6 years on the Kohs test. The least intellectual impairment was shown by patient A1, who suffered from subcortical motor aphasia. He had most insight, conducted himself in fairly intelligent fashion, obtained moderate scores on a variety of performance tests and had a mental age of 11 years 9 months on the Kohs test.

12. Lidz, T.: The Amnestic Syndrome, Arch. Neurol. & Psychiat. **47**:588 (April) 1942.

Measurement of Improvement: The rise in the Kohs mental age as clinical improvement occurs appears to be significant proof of the capacity of the test to measure the intelligence possessed at the moment. When one is following the course of a patient with intellectual deficit or is measuring intelligence before and after an operation on the brain, fever therapy or shock treatment, there is no need to compare the vocabulary and the Kohs score, for the interest lies in the difference between the intelligence scores at the time of the measurements. Repetitions of the Kohs test will be useful for this purpose if the apparent sensitivity to slight alterations in intelligence is confirmed.

The clinical improvement of 3 patients was followed. Patient 1, who was suffering from dementia paralytica, was unable to complete any block designs even though rapport was sufficient for him to score a mental age of 9 years on the Binet test and a mental age of 10 years on the vocabulary test. Shortly after the completion of malarial therapy the Kohs mental age rose to 6 years 6 months, the Binet mental age to 9 years 4 months and the vocabulary mental age to 12 years; he was still extremely delusional, and the intellectual deficits were pronounced. Several months later, though some deficits remained, he was free of delusions and was considered as socially recovered; the Kohs mental age had risen to 9 years 6 months, while the Binet and vocabulary scores remained unchanged. Patient 20 was severely deteriorated after carbon monoxide poisoning; at the time when clinical improvement was becoming definite the Kohs mental age was 10 years 6 months; six weeks later, when he was almost completely recovered, the Kohs mental age was 15 years 3 months. Patient A 5, who was almost totally aphasic after sustaining a small laceration in the temporoparietal region of the brain, could not complete the simplest Kohs design. The gradual rise in the mental age, as recorded in table 2, corresponded to the improvement in speech, comprehension and ability to perform on various qualitative tests of his intelligence. Seven months after the injury he had become capable of returning to a simple occupation, could grasp four and five part commands and could make himself understood fairly well; the Kohs mental age had reached 11 years.

Patients with Doubtful Deterioration.—The patients in group 1 were definitely deteriorated as a result of structural damage to the brain. There were 7 patients concerning whom there was reasonable doubt, for a variety of reasons. The Kohs test appeared to be a valuable aid in the measurement of the intelligence of all these patients, but for the purposes of this paper the status was determined not by the test but by clear clinical evidence of other types. The data for the group are given in table 3.

It was considered possible that patients D 1 and D 2 had deteriorated after prolonged alcoholism and injury to the head, respectively, but there was no reason to believe that the low intelligence was due to anything other than poor native endowment; the school records had been poor, and there was no clear evidence of deterioration. Patient D 3 had been admitted to the clinic with a

diagnosis of post-traumatic confusional state. It was found that he was very deaf and that his education had suffered greatly. The Kohs mental age was more than 4 years higher than the mental age on the vocabulary test, as might be expected with an intelligent deaf person. With reassurance and the settlement of a few personal problems, the symptoms cleared within a few days. Patient D 4 had suffered a cortical laceration, causing motor aphasia and alexia and paresis of the right arm. At the time of the examination the aphasia had disappeared completely, and the family did not think that any intellectual impairment remained. The Kohs mental age was 2 years higher than the vocabulary mental age, and the integrity of his intellect has been borne out by subsequent achievement. Patient D 5 was a youth who suffered from manic and depressive swings. Despite a Binet mental age of 15 years 8 months and a vocabulary mental age of 17 years, he appeared bland and unintelligent. The Kohs mental

TABLE 3.—*Measurement of Intelligence of Patients with Doubtful Deterioration*

Case No.	Age, Yr.	Education	Occupation	Diagnosis	Mental Age			
					Binet	Vocabulary	Kohs	Vocabulary Minus Kohs
D1	48	5th grade	Printer	Chronic alcoholism	9-8	10	8-9	1-3
D2	43	4th grade	Carpenter	Post-traumatic state (?)	9-10	10	11-2	—1-2
D3	17	High school (2 yr.)	Mechanic	Post-traumatic state; deafness	13-8	13	17-8	—4-8
D4	20	High school	Student	Recovery from motor aphasia; cortical laceration	16-9	16	18-0	—2-0
D5	21	High school	Student	Manic-depressive psychosis; metrazol deficit (?)	15-8	17	12-0	5-0
D6	49	College	Executive	Recovery from aphasia; meningioma removed	15-6	16	13-4	2-8
D7	20	Some high school	Student	Schizophrenia and epilepsy	11-1	14	11-2	2-10

age of 12 years seemed more in harmony with his behavior. It appeared likely, but it could not be proved, that metrazol treatment during a manic episode had left permanent impairment. Patient D 6 had recovered from severe hemiparesis and aphasia after a meningioma was removed, but suffered from occasional convulsions. He expressed the belief that he was not as keen as he had once been, which was not unlikely, but there was no objective evidence other than a difference of 3 years 8 months between the mental ages on the Kohs and vocabulary tests. Patient D 7 was a schizophrenic girl who also suffered from generalized convulsions and had localized electroencephalographic changes. As it was uncertain whether the obvious deterioration was due to the lesions in the brain or to the schizophrenic condition, the case is included here.

Schizophrenic Patients.—The group of 15 patients does not purport to be representative of schizophrenic patients. They were tested as part of a study of the thinking of such patients relatively early in their illness. None was severely disorganized or too withdrawn to permit

the establishment of satisfactory rapport for the purpose of testing. The results of the tests cannot be generalized for all patients with schizophrenia, but the figures include the results for all the patients examined.

The data for the 15 patients are given in table 4. The mean mental ages of the patients were: Binet, 15.9 ± 0.4; vocabulary, 15.5 ± 0.5; Kohs, 16.1 ± 0.5. The differences in the mental ages are not significant, particularly as the vocabulary mental age was arbitrarily kept 6 months

TABLE 4.—*Measurement of Intelligence of Patients with Schizophrenia*

Case No.	Age, Yr.	Education	Occupation	Diagnosis	Mental Age: Binet	Vocabulary	Kohs	Vocabulary Minus Kohs
S 1	20	7th grade	Housewife	Schizophrenia	10-11	10	11-9	—1-9
S 2	17	High school (3 yr.)	Student	Schizophrenia	14-3	14	12-1	1-11
S 3	51	5th grade	Laborer	Schizophrenia	11-10	13	12-6	0-6
S 4	22	High school	Housewife	Schizophrenia	13-7	12	13-7	—1-7
S 5	25	High school	Mechanic	Schizophrenia	16-10	16	14-3	1-9
S 6	28	High school	Executive	Schizophrenia episode	17-2	17	16-7	0-5
S 7	24	High school	None	Schizophrenia	18-0	18	17-6	0-6
S 8	17	High school (3 yr.)	Student	Schizophrenia	16-1	14	18	—4-0
S 9	16	High school (3 yr.)	Student	Schizophrenia	14-10	14	18	—4-0
S10	48	High school	Mechanic	Schizophrenia	18-0	16	18	—2-0
S11	40	College (1 yr.)	Rancher	Schizophrenia	16-2	16	18	—2-0
S12	34	College	Reporter	Schizophrenia	18-0	18	18	0
S13	30	College	Lawyer	Schizophrenia	18-0	18	18	0
S14	27	High school	Reporter	Schizophrenia	16-10	18	18	0
S15	22	High school	Mechanic	Schizophrenia	18-0	18	18	0

Biometric Constants

Binet mental age	m = 15.9 ± 0.4	S. D. = 2.3 ± 0.3
Vocabulary mental age	m = 15.5 ± 0.5	S. D. = 2.5 ± 0.3
Kohs mental age	m = 16.2 ± 0.5	S. D. = 2.5 ± 0.3
Difference between mental ages in vocabulary and in Kohs test	m = —.7 ± 0.3	S. D. = 1.8 ± 0.2

below the actual level by scoring it in terms of the exact year, without the addition of months.

Chart 2 shows the scatter of the individual cases when the Kohs mental age was plotted against the vocabulary mental age. In no case was the Kohs mental age as much as 2 years lower than the vocabulary mental age. Only 2 patients showed a Kohs mental age more than 6 months lower than the vocabulary mental age, and these 2 patients were among those treated with shock therapy.

In the group of schizophrenic patients no essential difference appeared between the Kohs and the vocabulary mental age, and the results are similar in this regard to what would be anticipated for a

group of normal persons. The group furnishes something of a control on the series with cerebral deficits. The excellent performances indicate that delusion formation and personal preoccupations do not by themselves affect the ability to perform on the Kohs test. Except for patients 18 and 19, of the cerebral deficit series, there was no overlap between the performances of the patients in the two groups.

These observations are not in agreement with those of Bolles and Goldstein,[7] who found schizophrenic patients incapable of adopting an "abstract" approach, including inability to solve the simpler patterns of the Kohs block test. It is clear that their results cannot be considered typical for schizophrenic patients as a group. The present

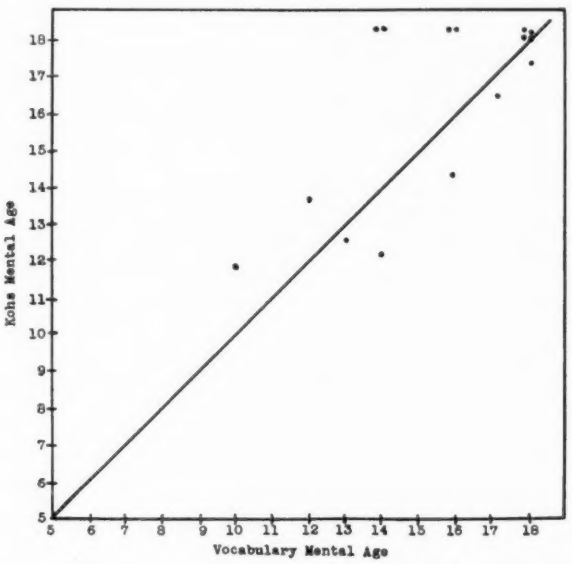

Chart. 2.—Correlation of mental ages in the vocabulary and in the Kohs test in 15 cases of schizophrenia.

series shows that many schizophrenic patients are capable of a high order of impersonal abstraction. It may be added that one of the patients with the most chronic form of the disease, who showed habit deterioration, turned in the finest performance on the Kohs test ever seen by the examiners.

Good performances of schizophrenic patients are not often reported in the literature, evidence in support of the belief that deterioration akin to that following damage to the brain occurs. The wide divergence in ability to form the Kohs designs between schizophrenic patients and those with cerebral lesions indicates that tests planned to measure intellectual deterioration had best differentiate between these two types of thinking disorder.

LIMITATIONS OF THE PROCEDURE

As has been mentioned, certain patients suffering from amnestic difficulties show little impairment in intelligence when there is no need to recall material or to perform sequentially. Attention is called to the necessity of supplementing tests, such as the procedure presented by the use of memory tests, whenever the possibility of amnestic difficulties exists.

A second limitation occurs when one is dealing with elderly persons. The ability for active reflection declines with advancing age,[1] and some persons past middle life show lower performance on the Kohs test than on the vocabulary test even though no specific lesions are present. Under many circumstances the decline of intellectual abilities that occurs with age is precisely what one wishes to measure. One may wish to know whether loss of intellectual control contributes to eccentricities of behavior and how marked is the falling off of cortical capacities as a person approaches senescence. However, when the information sought concerns the result of a specific injury to the brain in elderly persons, whether or not a vascular accident or a head injury has caused deficit, the test is of limited value. It can be estimated from Wechsler's graphs concerning the decline of assets with age [1] that at the age of 50 years the Kohs mental age will be but 80 per cent of the vocabulary mental age and at the age of 60 but 70 per cent. A person 60 years old with a vocabulary mental age of 16 years may have a Kohs mental age of but 11 or 12 years. Thus, in the case of a man of 74, such as patient 11, the contrast between the vocabulary mental age of 14 years and the Kohs mental age of 9 years indicates the falling off of intellectual abilities with age and senile changes in the brain, but cannot be taken to signify that a specific cerebral lesion exists.

SUMMARY

The Kohs block test offers a means of measuring the intelligence of persons suffering from intellectual deficits after cerebral damage, as it tests the functioning of the intellect at the moment, relatively free from the influence of material which had been acquired prior to damage to the brain. With 5 aphasic patients and with 21 patients suffering from cerebral deficit states the test appeared to afford a good index of the intellectual resources. In 3 patients the clinical improvement was paralleled by appropriate increases in the score on the Kohs test.

As a test for the presence of deterioration the performance on the Kohs test is contrasted with the score on a vocabulary test. The advantages and limitations of the procedure are discussed. Twenty patients suffering from definite cerebral lesions with deterioration showed a mean difference of 4.2 years between the mental age on the

vocabulary test and that on the Kohs test. Fifteen patients with schizophrenia showed no significant mean difference between the mental ages as determined by the two tests. Of 21 patients with deterioration due to cerebral lesions, all except 2 showed a difference of at least 2 years 4 months between the vocabularly and the Kohs determinations of the mental ages. None of the 15 schizophrenic patients showed a Kohs mental age as much as 2 years lower than the vocabulary mental age.

On the basis of the material, it is suggested that when the mental age on the Kohs test is equal to or higher than the mental age on the vocabulary test it is unlikely that the patient is deteriorated unless a specific memory deficit is present. As the distribution curve and scatter for persons with intact brains are not known, it cannot be stated exactly what degree of difference between the vocabulary and the Kohs determination can be taken to signify a cerebral lesion. However, the test has shown itself a reliable adjunct to clinical studies, and even in its present state it suggests that when the Kohs mental age is more than 2 years lower than the vocabulary mental age, cerebral defects impairing the intellectual functioning should be considered. Greater differences add to the evidence proportionately.

The excellent performances of the schizophrenic patients on the Kohs test indicate that such patients may be capable of a high order of impersonal abstraction and may show no impairment of general intelligence. The thinking disorders of schizophrenic patients should not be included in uncritical fashion with the disabilities following damage to the brain.

Johns Hopkins Hospital.

CONGENITAL ATRESIA OF THE FORAMENS OF LUSCHKA AND MAGENDIE

JOHN K. TAGGART JR., M.D.
AND
A. EARL WALKER, M.D.
CHICAGO

The existence of the foramens of Luschka and Magendie has been the subject of controversy in the past. Hence it is not surprising that confusion has arisen regarding congenital abnormalities of these structures. While certain earlier writers (Sutton; Dandy and Blackfan) accurately described the phenomena that may arise if the foramens do not develop normally, recent authors (Pines and Surabaschwili; Castrillón; Sahs) have failed to recognize the pathology so produced. For this reason a detailed discussion of the clinical and pathologic aspects of congenital atresia of the foramens of Luschka and Magendie seems pertinent.

HISTORY

Few cases of this anomaly have been reported. Certain articles published in the latter half of the nineteenth century were probably concerned with this condition, but owing to inadequate descriptions it is impossible to be certain of their classification (von Recklinghausen). Virchow referred to and illustrated a hydrocele of the fourth ventricle but did not give further details of the anomaly. The cases of Fusari (1891) and Rossi (1892) appear similar and are probably examples of this condition.

The more recently reported cases are described in detail, and a brief abstract of each is appended.

Case of Dandy and Blackfan.—A 13 month old child had been well until 9 months of age, when she had a severe illness lasting four weeks, characterized by high fever, severe opisthotonos and many convulsions. The child had been delivered instrumentally at term. On examination the head was found to be enlarged, with open fontanels and diastasis of the sutures. Lateral and vertical nystagmus was present. Bilateral papilledema of 1 to 2 diopters was seen on ophthalmoscopic examination. Studies of the spinal and the ventricular fluid revealed no abnormality. Evidence of a block between the ventricles and the subarachnoid space was revealed by the phenolsulfonphthalein test. The child died one month later.

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From the Division of Neurological Surgery, the University of Chicago.

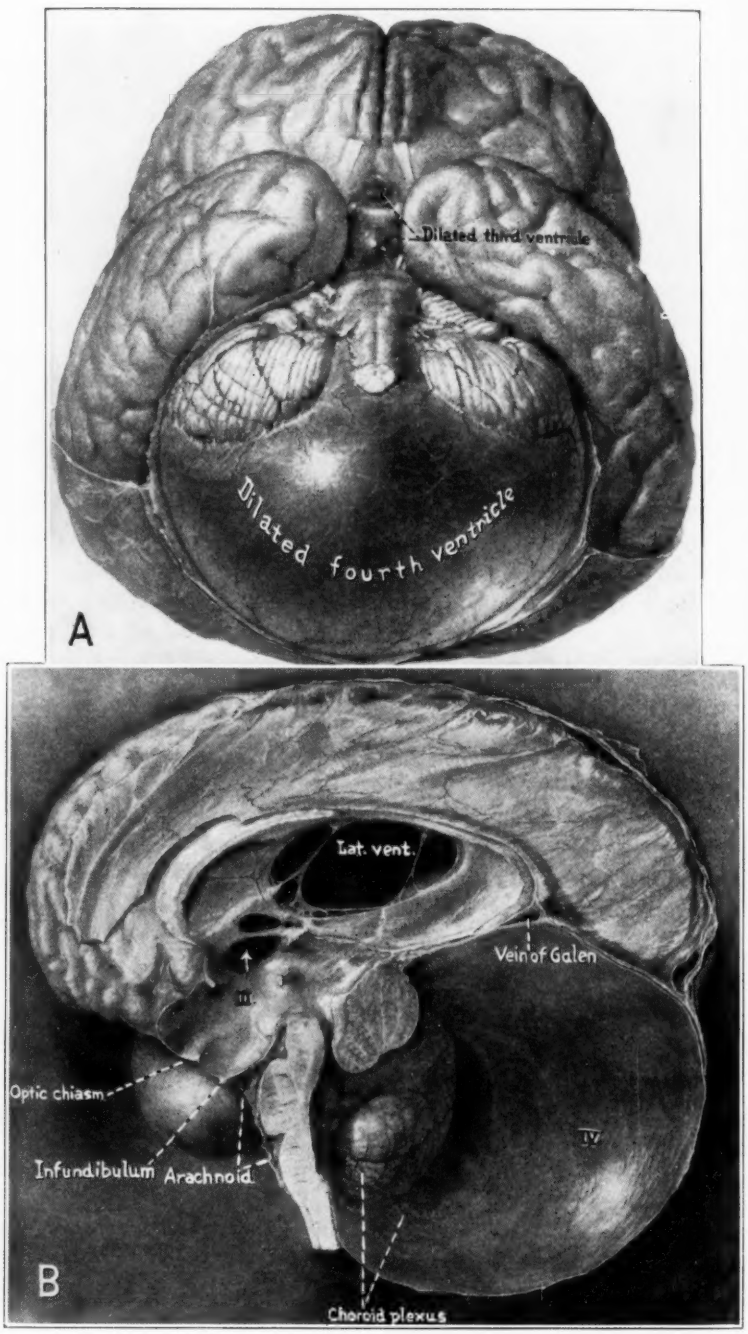

Fig. 1.—The base and a midsagittal section of the brain in Dandy and Blackfan's case of congenital atresia of the foramens of Luschka and Magendie. The dilated fourth ventricle and the internal hydrocephalus are well shown. Note the nubbin of cerebellar vermis in the anterosuperior corner of the fourth ventricle. (Reproduced by permission of Dr. Walter E. Dandy.)

At necropsy the posterior fossa was observed to be filled with a huge, thin-walled cyst, the walls of which were continuous with the ependymal lining of the fourth ventricle. The entire ventricular system was dilated. The choroid plexus of the fourth ventricle lay in the cyst. The foramens of Magendie and Luschka were not patent (fig. 1).

In a subsequent communication (1921) Dandy stated that he had seen 3 other such cases but gave no details of them.

Case of Pines and Surabaschwili.—The patient, a 24 year old imbecile, had no interest in his surroundings, was unable to articulate clearly and was incontinent of urine and feces. Except for his mental status, the neurologic examination revealed nothing abnormal. He died of hemorrhagic enterocolitis and chronic glomerulonephritis.

Examination of the brain revealed marked dilatation of the fourth ventricle with displacement of the cerebellar hemispheres laterally and the anterior vermis rostrally. The posterior portion of the cyst was covered by a thin membrane, which was continuous with the arachnoid of the cerebellum and the ependyma of the fourth ventricle. The state of the foramens of Luschka and Magendie was not mentioned. Except for atrophy of the right dentate nucleus, the cerebellar nuclei were normal. The left inferior olivary nucleus was aplastic. The vermis was defective, only the lingula, the central lobe, the culmen and the anterior part of the declive being present.

The case was considered an example of aplasia of the vermis cerebelli.

Case of Castrillón.—A woman aged 59, a housewife, had always been mentally retarded. After the birth of her second child she had attacks of dizziness, severe frontal headache and vomiting. Four weeks before admission to the hospital the symptoms became more intense. Physical and neurologic examinations revealed little abnormality. The Wassermann reaction of the blood was positive. Roentgenograms of the skull were said to be normal. She was given intramuscular injections of a bismuth compound but became worse and died.

At autopsy the fourth ventricle was observed to be enormously dilated and covered posteriorly by a thin membrane, which merged with the pia-arachnoid. The third ventricle was enlarged. The posterior portion of the vermis, the flocculus and the paraflocculus were not present. The dorsal accessory olivary nucleus was absent. The foramens of Luschka were patent.

The case was regarded as an example of congenital aplasia of the cerebellar vermis.

Case of Scarff.—A 16 month old baby had right hemiplegia and choked disks. A ventriculogram showed pronounced and symmetric hydrocephalus of the lateral and third ventricles. Exploration of the posterior fossa revealed a large cyst replacing the cerebellar vermis.

The cyst wall was removed, and the patient made an uneventful recovery. The inclusion of this case without further data might be contested. It seems similar to the previous cases and to those we have seen.

Case of Sahs.—A 16 year old boy had developed normally until 12 months of age, when he had a generalized convulsive seizure. At 6 years of age he began to have attacks in which he would suddenly throw his head to the left and whirl around once or twice. When he was 16 years old he engaged in a "neck-strengthening contest." The following day he was very dizzy and complained of headache and pain in the neck. After a short interval of improvement he became much worse. Neurologic examination revealed nothing abnormal except for moderate nuchal rigidity and an ataxic gait. Lumbar puncture showed no

abnormalities. The spinal fluid gave a slightly positive Pandy reaction. Roentgenograms of the cervical portion of the spine and the base of the skull were interpreted as normal.[1] After two attacks of sudden apnea with bradycardia papilledema and nystagmus developed.

Exploration of the posterior fossa by Dr. O. R. Hyndman revealed a huge cyst occupying the posterior fossa. The cerebellar hemispheres were widely separated, and the vermis appeared to be absent. The fourth ventricle opened widely into this cystic cavity. After operation the patient grew steadily worse and died of pneumonia and bulbar paralysis.

At autopsy the vermis was observed to be compressed and distorted. The anterior vermis appeared to have attained almost normal development, but the posterior vermis was rudimentary, although all the structures were represented. The fourth ventricle was hugely dilated and lined by a thin membrane, "which was attached to the vermis anteriorly, extended outward to the lateral aspect of each cerebellar hemisphere and then reached posteriorly and inferiorly as far as the medulla. The lateral recesses of the fourth ventricle were patent" (Sahs, page 55).

Microscopically no abnormality was noted in the pons, medulla, spinocerebellar tracts, cerebellar peduncles or cerebellar nuclei. The vermis was poorly myelinated, and while the three layers of the cerebellar gray matter were readily identified, the Purkinje cell layer in places was sparse or absent. The cytoarchitecture of the hemispheres was normal.

Case of Cohen.—A 13 year old, mentally retarded boy was subject to headaches associated with a feeling of falling to the left. On one occasion diplopia and vomiting had occurred.

Neurologic examination revealed a positive Macewen sign, a dilated right pupil and weakness of the external rectus muscle. Papilledema of 1 D. was present bilaterally. There was slight weakness of the left side of the face of central type. The gag reflex was depressed. Rapid alternating movements were defective, especially on the left. The deep tendon reflexes were decreased in the upper extremities and increased in the lower.

The cerebrospinal fluid pressure was 330 mm. of water and was otherwise normal.

Roentgenograms of the skull were interpreted as showing "a large skull with some separation of the fronto-parietal sutures."[2] Ventriculography was attempted, but a cyst was encountered. Sufficient air entered to demonstrate roentgenographically dilated ventricles and a huge cyst in the posterior fossa. After this procedure the patient complained of increasing headaches, and the papilledema became more severe.

The posterior fossa was explored through an occipital bone flap. A thin vascular membrane continuous with the fourth ventricle was observed to enclose a cyst that occupied the entire enlarged posterior fossa. A similar membrane extended at right angles to the first, dividing the upper part of the cyst into two chambers. One membrane lined the posterior fossa and ended in a closed pocket over the spinal cord. It was intimately attached to the pons and medulla. In the anterosuperior portion of the cyst the iter could be seen. On either side of the brain stem were two small nubbins of cerebellar tissue. No mention was

1. Through permission of Dr. Sahs, we have had the privilege of examining the roentgenograms. Unfortunately, the lateral views do not include enough of the base of the skull to permit one to determine the position of the lateral sinus.

2. Through permission of Dr. Cohen, a roentgenogram of the skull of this patient is reproduced in figure 11.

made of the vermis. The tentorium was attached halfway between the normal positions of the coronal and lambdoid sutures. The cyst wall was partially removed. The patient recovered after a rather stormy postoperative course.

Sections of the cyst wall showed it to be composed of two layers. The first resembled undifferentiated leptomeninges, and the second contained neuronal and glial elements with remnants of ependyma. In some sections there was fusion of the ependymal and meningeal layers to form a "choroid plexus–like structure."

REPORT OF CASES

To the previously mentioned cases collected from the literature we add 3 of our own.

CASE 1.—S. A., a girl 5½ years of age, was admitted to Bobs Roberts Memorial Hospital on May 23, 1934 with the complaint of inability to walk, loss of weight and anorexia of three weeks' duration.

History.—The child was born two weeks prematurely but had a normal development. She sat up at 7 months, talked at 14 months and walked at 16 months of age. From the age of 1 month the parents had noticed gradual enlargement of her head. When 3 years of age she began to complain of occasional headache, usually accompanied by vomiting.

Approximately five weeks before admission the child became much worse, with persistent headache and vomiting several times a day. At the same time the parents noticed a pulsating depression in the occipital region. Two weeks later the patient was unable to walk without assistance and showed a tendency to fall to the left.

Examination.—On admission to the hospital the child was lethargic and uncooperative. There was a small pulsating mass in the occipital region of the skull, over which a bruit was heard and a thrill was palpable at times. There was cracked pot resonance on percussion of the skull. The head measured 55 cm. in its largest circumference.

The optic fundi showed bilateral papilledema of 2 D., with hemorrhages. The veins were large and tortuous. There was slight weakness of the right side of the face. The deep tendon reflexes were extremely sluggish, and the abdominal reflexes were absent. The right plantar reflex was extensor and the left flexor.

All extremities were moved equally well, but there was pronounced hypotonia, more so on the right.

There was marked nuchal rigidity with moderate opisthotonos. The gait was slightly unsteady, and the patient walked on a wide base.

Roentgenograms of the skull revealed prominent sutural diastasis, thinning of the bone in the superior occipital region and pronounced enlargement of the posterior fossa. The petrous ridge passed onto the lower margin of the parietal bone, and the impression of the lateral sinus followed along the inferior part of the parietal bone instead of in its normal position on the occipital bone (fig. 2).

Operative Procedure.—On May 25, 1934 a ventricular puncture, performed by Dr. P. C. Bucy, revealed a pressure of 350 mm. of cerebrospinal fluid. After the puncture the child's condition improved decidedly, with disappearance of the opisthotonos and stupor. Four days later a suboccipital craniectomy was attempted, but convulsions supervened and the operation had to be discontinued. On June 1 a cerebellar puncture was made and 2 ounces (56 cc.) of clear fluid obtained.

The child still did not do well, and a week later the suboccipital region was explored. The dura mater was not under tension. It was incised and reflected downward, revealing an enormous cyst occupying the midline of the posterior

fossa. The cerebellar hemispheres lay on the rostral part of the cerebellar fossa on either side. At the bottom of the cystic cavity could be clearly seen the floor of the fourth ventricle, which was exposed from the calamus scriptorius to the dilated aqueduct of Sylvius. The cavity was obviously a greatly dilated fourth ventricle. In the upper part of the field the tentorium was extraordinarily thin,

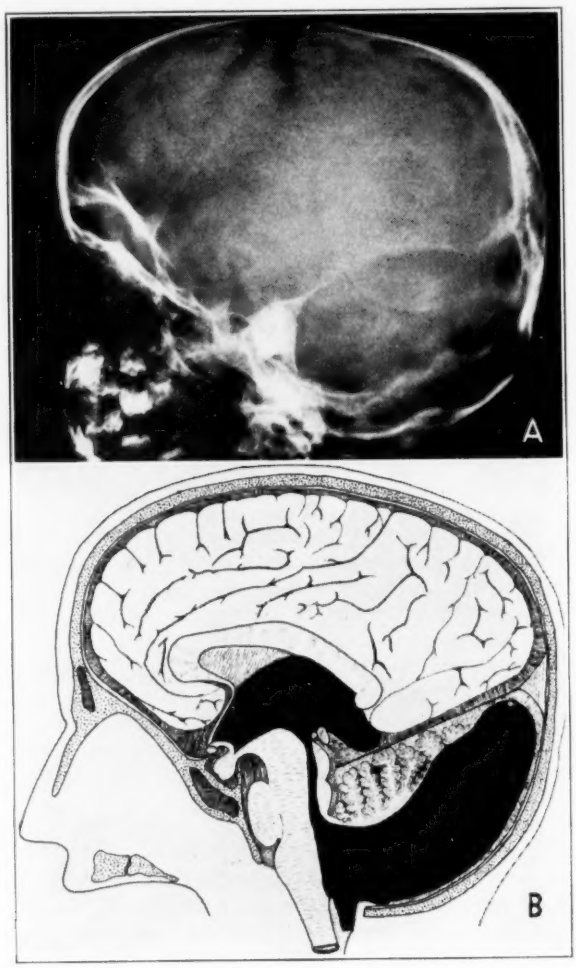

Fig. 2 (case 1).—*A*, lateral roentgenogram of the skull, showing the position of the lateral sinus on the inferior margin of the parietal bone and the enormous posterior fossa.

B, diagrammatic representation of the anomaly based on the operator's sketch and notes. The large dilated fourth ventricle and the compressed vermis cerebelli are well shown.

and the under surface of the occipital lobe could be seen clearly. In the antero-superior part of the cyst wall was the much thinned-out and compressed vermis, which was reduced to a thin layer of tissue. No choroid plexus was seen. The

dilated fourth ventricle extended down through the foramen magnum and beneath the arch of the atlas. The posterior arch of the atlas was therefore removed and the dura incised in the midline to expose this area. Just posterior to the dilated fourth ventricle, overlying the posterior part of the medulla, was a very small cisterna magna, which had a capacity of 1 or 2 cc. The wall of the cisterna magna was distinct from the wall of the fourth ventricle in this region. Posteriorly the wall of the fourth ventricle and the arachnoid were fused into one membrane, which was particularly thick and white in the area where one would expect to see the foramen of Magendie. On either side of the posterior part of the medulla could be seen a small lateral recess (fig. 2).

Small windows, about 5 to 10 mm. in diameter, were made in the walls of the fourth ventricle opening into the cisterna magna and the basal cisterns on either side in an attempt to reestablish the normal flow of cerebrospinal fluid.

Course.—The patient did poorly after operation. She never regained consciousness and died on the fourth postoperative day. Unfortunately, permission for autopsy could not be obtained.

Although the anomaly could not be examined histologically, study of the operative and roentgenologic observations enabled us to interpret the developmental defect.

CASE 2.—*History.*—J. A. F., a 13 month old girl, was brought to the Bobs Roberts Memorial Hospital on June 2, 1938 with a history of vomiting all feedings for ten days. About a month before onset of vomiting the patient had fallen a distance of approximately 4 feet (120 cm.). When picked up she was pale, did not cry and soon afterward vomited. She did not lose consciousness and had no convulsions. She soon appeared perfectly well, and for the next three weeks she walked, ran about and played as well as ever. The parents noticed no defect in vision or hearing.

Ten days before admission she began vomiting. Associated with the vomiting was retraction of the head. This was intermittent at first but in the few days preceding admission became continuous.

Examination.—At the time of admission the baby was semistuporous but resisted painful stimuli. The head was hydrocephalic, measuring 49 cm. in circumference, with deep-set eyes and a high forehead. The posterior half of the head was particularly prominent. The fontanels were open and very tense. The child lay in an extreme opisthotonoid position.

The pupils were round and equal, measuring 4 mm. in diameter, but reacted poorly to light. Occasionally vertical nystagmus could be elicited. The extraocular movements were full. The fundi appeared normal. The eyes did not follow a light, nor did the eyelids blink to a threatening gesture. The corneal reflexes were active and equal on the two sides. There was no evidence of facial weakness.

The baby responded to pinprick over the entire body. All four extremities were moved equally well. All deep tendon reflexes were active. When the head was turned to one side the contralateral arm and leg became slightly rigid, with a coincidental increase in the tendon reflexes.

Urinalysis and examinations of the blood, including the Wassermann test, revealed nothing pathologic.

Roentgenographic examination of the skull revealed diastasis of all cranial sutures. The digital markings were prominent. The impression of the lateral sinuses lay on the posteroinferior portion of the parietal bones, instead of on the occipital bones, as normally. The posterior fossa was hence enormously enlarged (fig. 3).

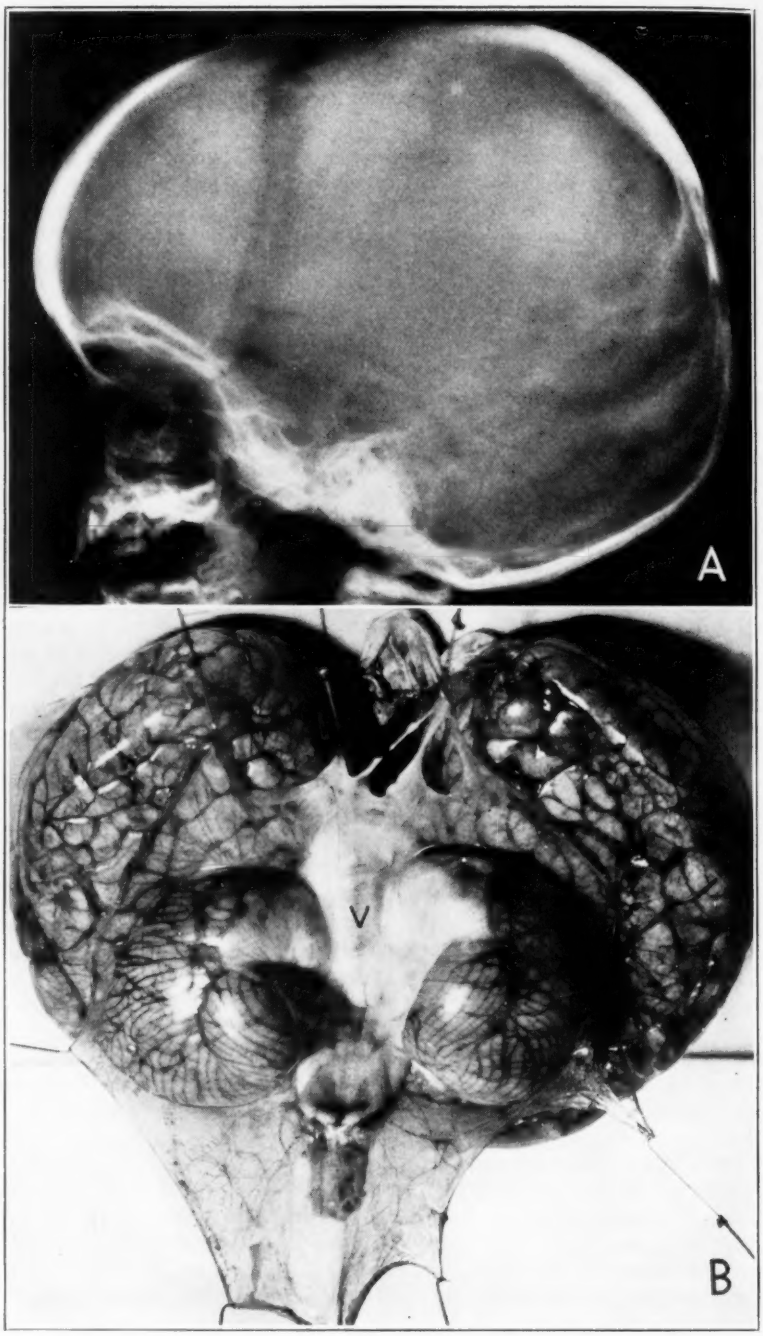

Fig. 3 (case 2).—*A*, lateral roentgenogram of the skull, showing the position of the lateral sinus and torcular Herophili on the parietal bone. The diastasis of the sutures is apparent.

B, dorsal aspects of the cerebellum, with the torn membrane of the fourth ventricle retracted to expose the ependymal lining and the compressed vermis (*V*).

Operation.—On June 2 a burr hole was placed in the right parietal region and a Frazier needle inserted into the ventricle. The child's condition immediately improved, and the retraction of the head disappeared.

It was believed that the fourth ventricle was enormously dilated, probably as a result of obstruction of the foramens of Luschka and Magendie, and it was decided to do a third ventriculostomy. This was performed by Dr. P. C. Bucy, but during the procedure the child's condition became poor and respiration ceased as the scalp was being closed.

Autopsy.—Complete autopsy was performed three hours after death by Dr. W. A. Stryker. The anatomic diagnoses were congenital cerebellar malformation, with enormous cystic dilatation of the fourth ventricle, due to obstruction of the foramens of Luschka and Magendie; fatty degeneration of the liver; dilatation of the right ventricle, and Meckel's diverticulum.

On removing the skull cap, the dura was observed to be extremely adherent to the superior longitudinal sinus, requiring separation by sharp dissection. There was a circular opening in the dura mater over the right frontal lobe at the site of the recent operation. The brain was removed intradurally. A large quantity of blood-stained cerebrospinal fluid escaped from the posterior fossa of the skull. On cutting the tentorium the posterior fossa was seen to be filled with what appeared to be an enormous, thin-walled cyst, the posterior wall of which was loosely adherent to the dura mater by short fine tufted strands and the anterior wall to the sides and dorsal surface of the pons and medulla. This thin membrane enclosed the greater part of the cystic cavity, which measured approximately 8.5 cm. in diameter and 5.5 cm. in depth. The membrane was continuous below with the floor of the fourth ventricle and above with the ependymal lining of the vermis and extended laterally over the surface of the cerebellar hemispheres. It was then reflected from the cerebellum to the dura of the posterior fossa. The vermis of the cerebellum above was compressed and flattened posteriorly to tissue paper thinness (fig. 3).

The fourth ventricle was lined by a grayish white, glistening tissue, which extended laterally onto the posterior surface of the cerebellum (a distance of 1 to 1.5 cm.) and superiorly onto the inner surface of the filmy membrane for about 2.5 cm. The cisterna magna could be demonstrated to be quite separate from the cystic cavity and appeared to be of normal size or smaller. At the point of attachment of the membrane to the lateral border of the cerebellar hemispheres there was a small tuft of choroid plexus, larger on the right than on the left. The cerebellar hemispheres had been pushed laterally and rostrally by the cyst and appeared as two small circular balls, having a maximum diameter of about 4 cm.

The aqueduct of Sylvius, 1.2 mm. in diameter, was slightly dilated. The third ventricle was moderately enlarged, being 7 mm. wide. There was slight dilatation of the foramen of Monro and practically no increase in the size of the lateral ventricles. They measured 3.6 cm. from the lateral margin of one ventricle to the same point of the other in a coronal section through the posterior part of the columns of the fornix. A perforation through the septum pellucidum connected the lateral ventricles directly with one another. Otherwise, grossly the cerebral hemispheres appeared normal.

Microscopic Study.—The cerebellum and the brain stem from the mesencephalon to the cervical portion of the spinal cord were embedded in one piece and sectioned serially. Every twelfth section was saved, and every twenty-fifth section was stained by the Nissl technic and the remainder by the Smith-Quigley method for

myelin, or in a few instances by Perdrau's technic for reticulin. Representative sections were taken from the cerebral cortex and the basal ganglia and stained for cells and myelin by the aforementioned methods.

Examination of the serial sections allowed differentiation of the lobules of the cerebellar vermis. The lingula could be readily identified, owing to its peculiar location. The lobulus centralis was present and appeared normal. Just above this portion of the vermis the culmen could be recognized. By following successive serial sections the primary fissure could be traced from its lateral position anteriorly to the midline, where it became continuous with the one on the opposite side. The declive thus could be recognized, and in more posterior sections the folium and the tuber. Shortly caudal to the lobulus tuberis a cleft appeared just to one side of the midline, in the substance of the white matter of the lobulus. This cleft was continuous with the fourth ventricle and the large cyst. Further posteriorly a second, and similar, cleft appeared on the opposite side of the midline, so that a midline folium projected posteriorly into the dilated fourth ventricle from the

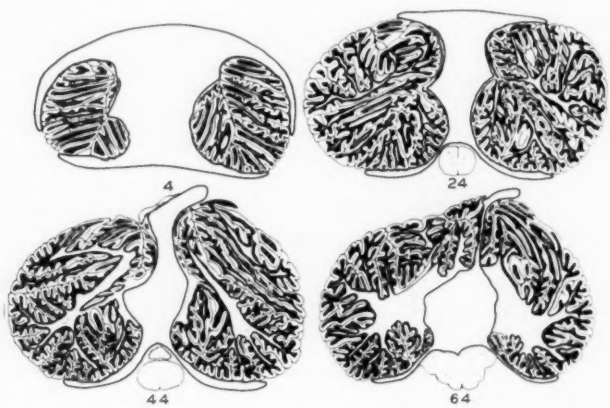

Fig. 4 (case 2).—Drawings of four representative sections of the cerebellum and brain stem, showing the attachment of the membrane covering the fourth ventricle.

tuber. Whether this represented a further division of the vermis or was merely a part of the tuber could not be determined with certainty. Thus the pyramid, the uvula and the nodulus were practically absent (fig. 4).

The pattern of the cerebellar folia was normal. The arachnoid was not thickened, although an occasional lymphocyte was seen in its meshes. The molecular layer of the cerebellum was well developed, and there was no evidence of the Obersteiner layer. The Purkinje cells were numerous and morphologically normal. The granular layer was dense and of about normal thickness. The white matter of the folia and the deep white matter of the cerebellum presented no abnormalities.

The hilus of the dentate nucleus was everted, owing to the general dilatation of the fourth ventricle, so that the folds of the nucleus were less prominent than usual. The nucleus was well developed and was composed of a normal number of well stained cells. The emboliform nucleus, composed of cells resembling those of the dentate nucleus, appeared normal except for distortion. The globose nucleus was composed of smaller and more angular cells but appeared to have a

normal complement of cells. The roof nuclear mass was ill defined and appeared to be smaller than usual (fig. 4). There were two symmetrically placed heterotopias in the lateral and posterior part of the cerebellar white matter. They consisted of a group of neurons resembling those of the dentate nucleus (fig. 9). The inferior olivary nucleus was well developed and appeared to contain a normal complement of cells. The dorsal accessory nucleus was normal. The medial accessory olivary nucleus, although prominent, had fewer cells than normal in its posterior portion. The pontile nuclei were well developed and showed no abnormality.

The wall of the cyst was composed of two layers of tissue, which could be readily distinguished where the wall was thick, but where it was thin they were difficult to differentiate without special staining methods. The inner layer was composed of neural tissue and was continuous with the white matter and the ependymal layer of the fourth ventricle. The outer layer was composed of arachnoid. Between the two layers occasional blood vessels were seen. In places, especially near its attachment to the cerebellum, the inner layer was relatively thick and consisted of imperfectly formed cerebellar folia lined by ependyma. In the greater part of its extent, however, the neural tissue comprising the membrane consisted of one or two layers of glial cells and their processes, which could be distinguished from the outer layer of arachnoid only by special stains for reticulin. It was this layer of neural tissue, extending laterally from the ependymal surface of the cerebellum, that formed a thin sheet covering the arachnoid over the folia on the medial, lateral and posterior parts of the cerebellar hemispheres. At the line of contact of the cerebellar hemispheres with the dura this neural sheet was reflected from the cerebellar folia and, with a layer of arachnoid, formed the membrane which in life was contiguous to the dura of the caudal portion of the posterior fossa. From the midline rostrally, where the vermis was well developed, the line of reflection extended on each side obliquely in a lateral and posterior direction to reach the extreme lateral aspect of the cerebellar hemisphere near its caudal tip. It then followed the lateral surface of the cerebellar hemisphere inferiorly and rostrally to reach the angle between the cerebellum and the medulla, thus forming the lateral recess. The neural membrane, thickened at this point, fused with the ependyma along the taenia of the fourth ventricle. The neural membrane and arachnoid were, however, continued posteriorly, lying over the arachnoid membranes which formed the cisterna magna and the spinal subarachnoid space. These membranes were quite distinct and readily separable (fig. 5).

In the deep lateral recesses small tufts of choroid plexus were present. The foramens of Luschka and Magendie could not be seen.

The cyst was thus seen to be lined by a greatly thinned-out posterior medullary velum and its associated tela choroidea.

The lateral ventricles were only slightly dilated. The cerebral hemispheres and the basal ganglia appeared normal grossly. In some areas of the cerebral cortex there was rather marked rarefaction of the neurons, particularly in the third and fourth layers. The neurons contained vacuoles, and the cytoplasm stained rather diffusely. The cell processes were visible for long distances. Scattered along the ventricular wall were subependymal perivascular hemorrhages. The arachnoid occasionally showed slight thickening. Except for these changes, the cerebral cortex and the basal ganglia were histologically normal.

The roentgenologic appearance of the skull in this case suggested a preoperative diagnosis of congenital atresia of the foramens of Luschka and Magendie. In spite of this advantage the outcome was unsatisfactory.

It is interesting to note that at the time of postmortem examination the lateral ventricles were almost of normal size; certainly, they were not dilated, as was the fourth ventricle. This may be attributed in part

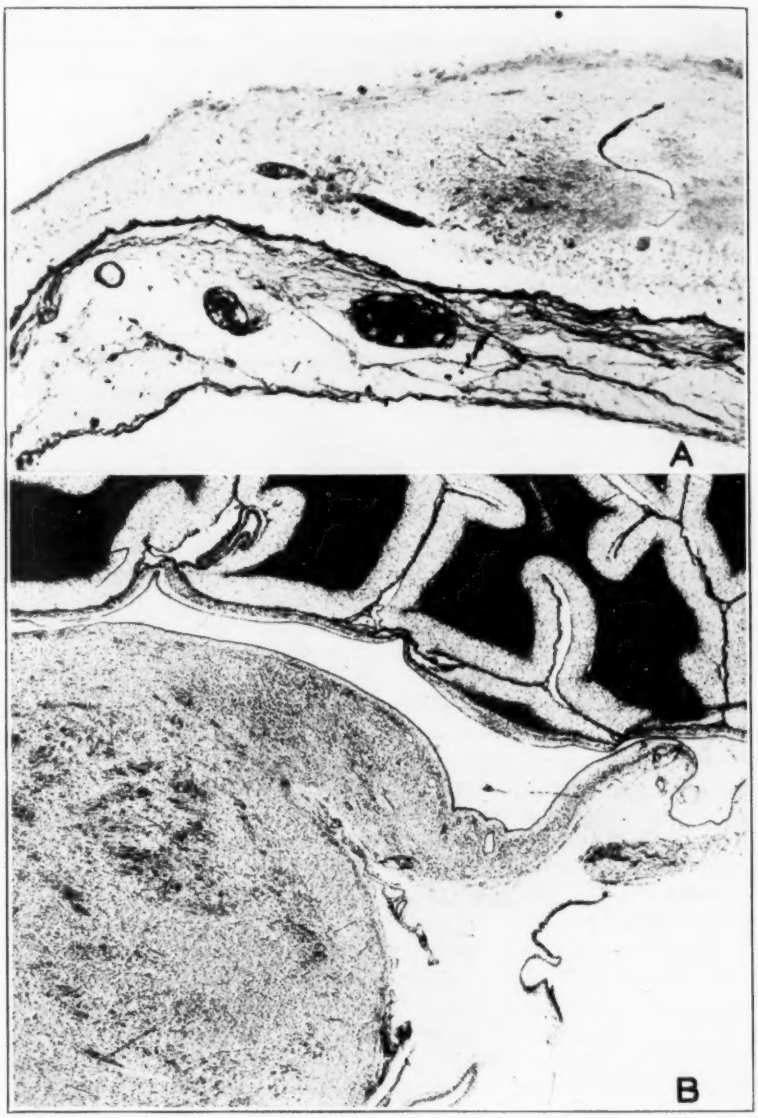

Fig. 5 (case 2).—*A*, photomicrograph of a thickened portion of the wall of the fourth ventricle, showing the neural membrane (above) and the arachnoid (below). Note the blood vessels in the subarachoid space. Perdrau preparation; × 135.

B, section through the medial portion of the lateral recess, showing the mode of its formation and a partial cerebellar folium lining it above. Nissl preparation; × 14.

to the use of a Frazier needle for continuous ventricular drainage and in part to the fact that compact cerebral hemispheres offered greater resistance than the poorly developed cerebellum.

CASE 3.—W. A., a white boy 10 months of age, was admitted to the Bobs Roberts Memorial Hospital on June 17, 1941 with the complaint of progressive enlargement of the head since birth. The patient had had a normal but rapid delivery, the entire duration of labor being one hour. Resuscitation was difficult, and for the first twenty-four hours the child seemed weak. The attending physician noted that the head was enlarged at this time. Roentgenograms of the chest were said to have shown moderate enlargement of the thymus. Measurements of the height and the circumference of the head and chest were taken at regular intervals in the next ten months, and the data are reproduced in the accompanying table.

The patient had 1 sibling, a healthy girl 3 years and 9 months old. Large heads were common in the family.

The child had had an adequate diet. He held up his head at 6 weeks and sat up at 8 months of age. The teeth had not appeared.

Data on Growth and Progressive Enlargement of the Head in Case 3

Date	Length, Cm.	Circumference of Head, Cm.	Circumference of Chest, Cm.
8/14/40	52	37	29.3
9/24/40	56.5	41	33.7
10/25/40	61	43	35.0
12/17/40	65.5	47	37.5
1/20/41	68	49	40.5
2/18/41	71	51	41.2
3/21/41	73	52	42.5
4/21/41	74.5	53	45.0
5/26/41	76.5	54.5	45.0
7/ 1/41	79	55.5	

Examination.—General physical examination revealed no abnormalities other than the considerable increase in the size of the head. The results of neurologic examination were normal except for a positive Macewen sign; the fontanels were bulging, and the veins of the scalp were dilated. The fundi oculi showed no pathologic change. Complete examinations of the blood and urine gave results within normal limits. A tentative diagnosis of hydrocephalus, probably noncommunicating, was made. No evidence of subdural collections of fluid could be found on puncture of the subdural space.

On July 1 both ventricles were punctured through the lateral angles of the anterior fontanels. Eighty cubic centimeters of fluid was removed and 70 cc. of air injected. Into the left lateral ventricle 5 cc. of phenolsulfonphthalein was injected, and almost immediately the fluid from the right lateral ventricle became red. After the taking of the ventriculogram the child was returned to his room and a lumbar puncture made. The spinal fluid was clear and colorless.

The ventriculogram demonstrated well filled and greatly enlarged lateral ventricles. The temporal and occipital horns were displaced dorsally and anteriorly. The third ventricle was dilated but was poorly demonstrated by the air. The impression of the lateral sinuses and the posterior continuation of the temporal ridge lay on the inferior part of the parietal bone instead of in their normal position on the occipital bone (fig. 6). This was interpreted as indicating

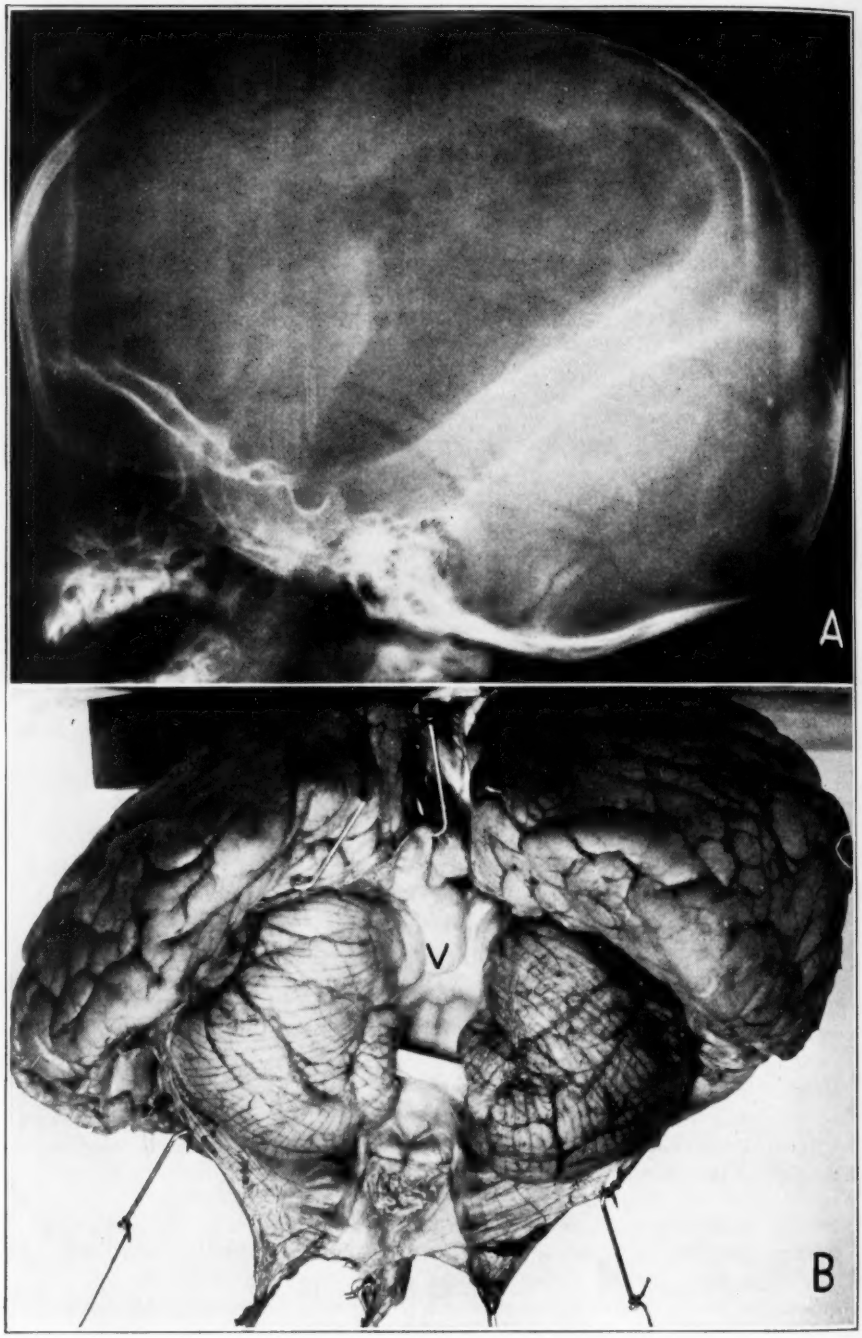

Figure 6

(See legend on opposite page)

enormous enlargement of the posterior fossa. The presence of congenital atresia of the foramens of Luschka and Magendie was considered but did not seem compatible with the absence of air in the fourth ventricle. The possibility of a large subdural hematoma in the posterior fossa was suggested, and it was proposed to puncture the posterior fossa through the dilated suture to establish the diagnosis.

Course.—After ventriculographic examination the patient became more irritable and severe opisthotonos developed. Respirations became labored, and in spite of supportive therapy the patient died, on July 3.

Autopsy.—Postmortem examination was performed by Dr. Eleanor Humphreys three and a half hours after death. The pathologic diagnoses were atresia of the foramens of Luschka and Magendie, with dilatation of the fourth ventricle and internal hydrocephalus; patency of the anterior and posterior fontanels; cranial tabes; enlargement of the posterior cranial fossa; acute dilatation of the right cardiac chambers; acute generalized passive hyperemia; slight pulmonary edema; asphyxial hemorrhages in the gastrointestinal mucosa; focal arteriolar nephrosclerosis (or healing glomerulonephritis [2]), and premature sclerotic changes in the coronary arteries and splenic arterioles.

On opening the intracranial cavity approximately 250 cc. of clear, straw-colored fluid escaped from a huge cystic space occupying the posterior fossa. This cavity appeared to be a greatly dilated fourth ventricle, for its walls were formed by a membrane continuous with the ependymal lining of the fourth ventricle. The membrane which formed the posterior half of the cyst wall was thin and translucent but separated readily from the dural lining of the posterior fossa. The brain (plus some fluid in the ventricles) weighed 1,030 Gm.

The cerebral hemispheres were large. The convolutions were flattened, but there was no other abnormality on the surface of the brain. The caudal tips of the occipital lobes projected 4 cm. posterior to the caudal portions of the cerebellar hemispheres. The posterior portion of the cerebellum was covered by a huge dilated fourth ventricle. The posterior and inferior surfaces of the cerebellum were covered with a membrane that was reflected from the cerebellar hemispheres along their posterosuperior and inferior margins onto the dura, forming the caudal part of the posterior fossa. Anteriorly this membrane became thickened, and it extended onto the vermis to become continuous with the lining of the fourth ventricle. Inferiorly the membrane passed from the inferior margin of the cerebellar hemispheres to the medulla to be attached at the margin of the calamus scriptorius. Over the cerebellum not covered by this membrane was what appeared to be normal arachnoid. It fused with the first-mentioned membrane as the latter was reflected from the cerebellum. A layer of arachnoid quite distinct from the other membrane could be seen forming a shallow cisterna magna, which was continuous with the subarachnoid space of the spinal cord. There was no gross

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EXPLANATION OF FIGURE 6 (CASE 3)

A, lateral ventriculogram, showing the internal hydrocephalus, the high position of the lateral sinuses and the torcular Herophili and absence of air in the fourth ventricle.

B, photograph of the dorsal surface of the cerebellum, with the membrane covering the fourth ventricle ruptured and retracted to show the lining of the ventricle and the compressed vermis cerebelli (*V*).

communication between the dilated fourth ventricle and the cisterna magna, and water placed in the fourth ventricle did not escape from either the foramens of Luschka or the foramen of Magendie (fig. 6).

The fourth ventricle measured 4 cm. in length and 2.5 cm. in width and was bounded laterally and posteriorly by the cerebellar tonsils, which were rounded protuberances on the medial surface of the cerebellar hemisphere. The floor of the fourth ventricle and the cerebellar vermis were covered by a grayish glial membrane, which passed laterally into the membrane over the cerebellar hemispheres, gradually thinning and disappearing. The floor of the third ventricle was dilated and thin. The lamina terminalis, likewise, was of tissue paper thinness.

Coronal section just posterior to the optic chiasm showed moderate internal hydrocephalus. The ventricles across the anterior horn measured 7 cm. Both foramens of Monro were enlarged. The third ventricle was greatly dilated, and the suprapineal recess extended posteriorly for a distance of 2.3 cm. The aqueduct of Sylvius was dilated and measured 3 mm. in diameter. There was a pronounced concavity on the medial and inferior aspects of both occipital lobes, into which the dilated fourth ventricle projected. The posterior horns were greatly dilated and measured 5 cm. in transverse diameter.

Superficially and on cross section the spinal cord appeared normal.

A midline incision was made in the cerebellum. It was possible to distinguish the lingula, the central lobule, the culmen, the primary fissure, the declive, the folium and a portion of the tuber. These lobules were pushed rostrally and compressed. There was no gross evidence of the posterior divisions of the vermis: the uvula, the pyramid and the nodule (fig. 10).[3]

Microscopic Study.—Serial coronal sections were made through the cerebellum and the brain stem at a thickness of 25 microns, and each twenty-fifth section was stained by the Smith-Quigley technic for myelin and the adjacent section was stained by Nissl's method.

The spinocerebellar tracts, cerebellar peduncles and pons appeared normal. The inferior olivary nucleus was normal, but the cells of the inferior portion of the medial accessory olivary nucleus stained poorly, were decreased in number and had bizarre outlines. The dorsal accessory olivary nucleus was normal.

In a section passing through the mesencephalon at the level of the oculomotor nucleus, the culmen, the primary fissure and a small portion of the declive could be recognized. The occurrence of these cerebellar structures at this level was undoubtedly due to the more cephalad position occupied by the cerebellum as a result of the pressure exerted from below by the hugely dilated fourth ventricle. Slight dilatation of the aqueduct of Sylvius was apparent, associated with mild ependymal proliferation.

Proceeding in a caudal direction, the dentate nucleus first appeared in a section passing through the pons just above the level of the trigeminal nerve. This nucleus was well developed. The cells were distinct, with fine granular cytoplasm. The nuclei were well defined and frequently eccentrically placed. The nucleoli were prominent and usually occupied a central position in the nucleus. The roof nuclei could also be seen at this level. They were rather poorly developed, with an ill

3. We realize that any attempt at division of a hypogenetic vermis cerebelli into its constituent lobules is open to criticism. It is difficult to be certain of the structure in the medial and posterior lobes. Comparison of our specimens with those of Dandy (1931) and Sahs shows that essentially the same lobules were present, although Sahs designated them somewhat differently.

defined outline. The cells were sparse and poorly stained, and in some cells the nuclei were absent altogether. Dorsal and medial to the dentate nucleus were two small collections of neurons that represented the globose nuclei. The individual cells appeared normal, but there was a notable decrease in the number of cells present. Medial to the dentate nucleus, another moderately well defined

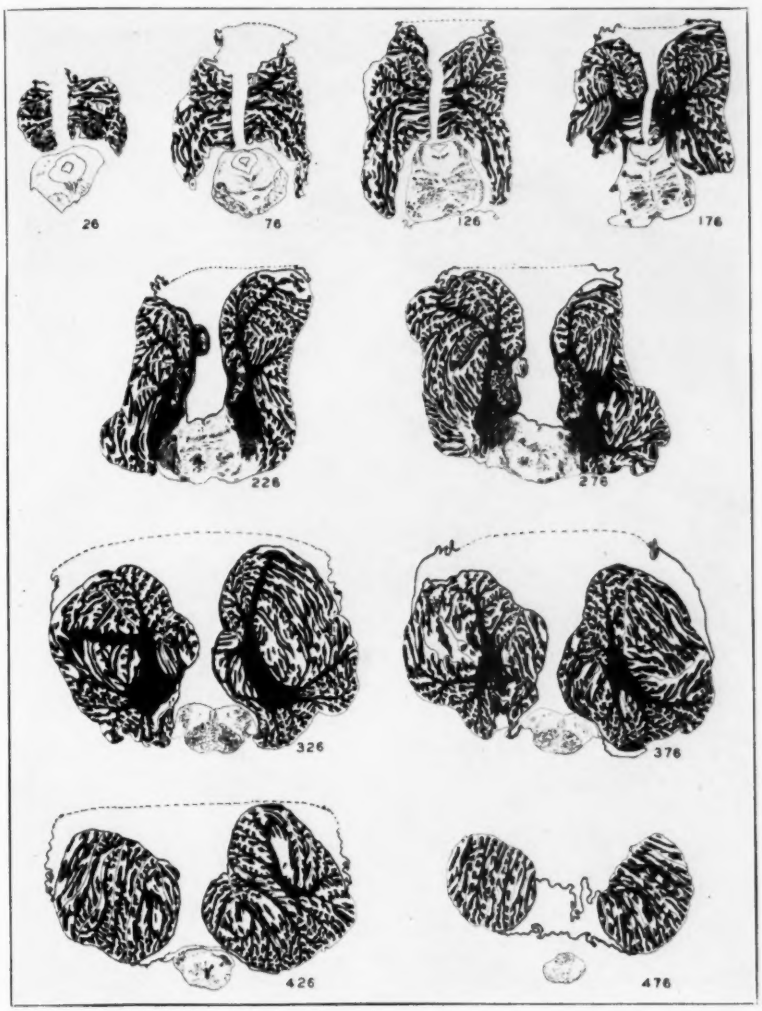

Fig. 7.—Representative serial sections of the cerebellum and brain stem, showing the enlarged fourth ventricle, the anterior portion of the vermis and the cerebellar hemispheres.

cellular mass represented the emboliform nucleus. The cells were not uniformly stained; otherwise they had the same appearance as the cells of the dentate nucleus.

In a section passing through the rostral border of the olive the midline structures of the cerebellum had disappeared. The cerebellar hemispheres, although distorted, appeared normal (fig. 7).

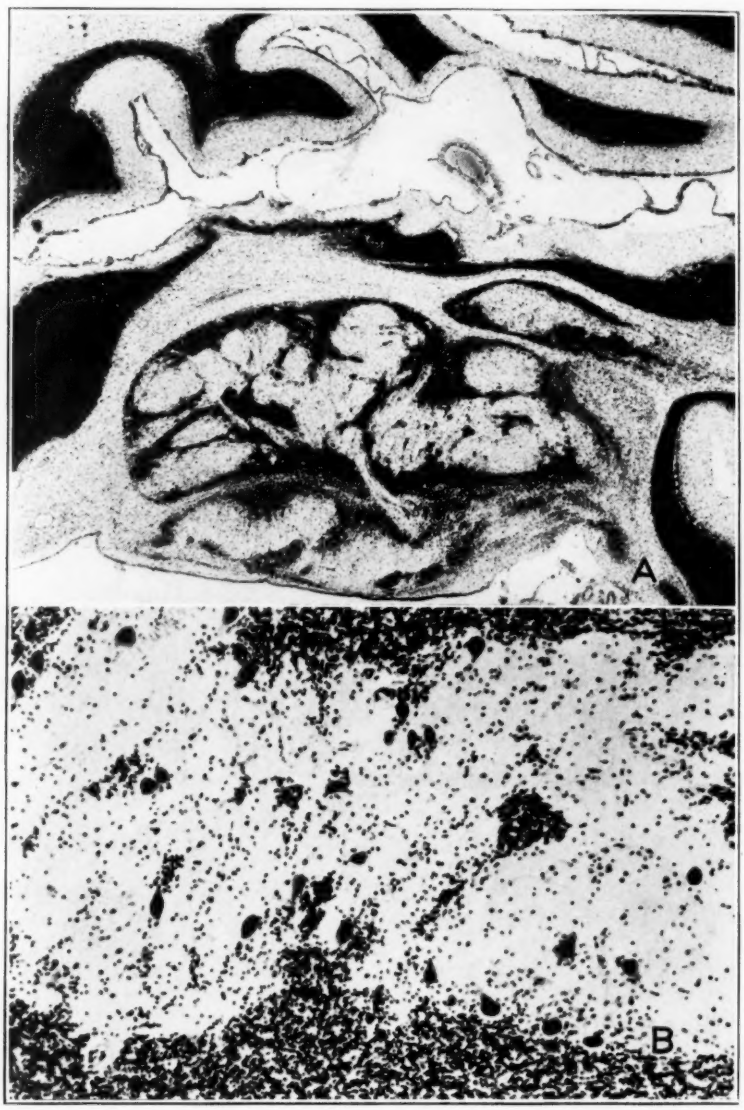

Fig. 8 (case 3).—Photomicrographs of the fetal lobule in the cerebellum. *A*, low power magnification (× 18), showing the general structure of the lobule. *B*, high power magnification (× 100), showing the dispersion of the Purkinje cells and the poorly developed granular layer. Nissl preparation.

On the ventromedial border of each cerebellar hemisphere there was a small lobule in the flocculus, containing primitive cerebellar tissue. In this area the neural

tissue was differentiated into the three layers seen in the normal folium and was arranged in a folial pattern, without sulci or arachnoid. The granular layer was moderately well developed in some areas, though in others it was thin or consisted only of irregular clumps of cells. The molecular layer was not bounded by arachnoid, and clumps of "granule" and Purkinje cells were dispersed throughout. The Purkinje cell layer was present but irregular, in places having few cells. There did not appear to be a core of white matter in these embryonic lobules (fig. 8).

In the posterior part of the deep cerebellar white matter on each side were two heterotopic masses of cells morphologically resembling the dentate nucleus. These masses lay just inside the margin of white matter and were circumscribed and oval to round in outline. The cells and the glial stroma were similar to those of the dentate nucleus (fig. 9). The cerebellar folia appeared normal at all levels except for the anomalies already described. The granular and molecular layers were well developed. The Purkinje cells were normal in number, appearance and staining qualities. The myelin seemed normal in amount and distribution. There was no apparent abnormality in the type or distribution of the vascular supply. The choroid plexus was small but was larger in the right lateral recess than in the left.

The membrane lining the cyst was composed of two layers of tissue: an inner neural layer and an outer layer of arachnoid. In some places the inner layer was differentiated into ependyma and in others into cerebellar tissue. The latter occurred where the membrane was contiguous with the cerebellar hemispheres. The cerebellar folia thus formed were imperfectly developed. The Purkinje cell layer was sparse and at times absent.

The arachnoid covering the outer portion of the cyst was composed of arachnoid externally and pia mater internally. Between the two layers there was in places a distinct space traversed by numerous thin strands of reticulin, which contained in their meshes a moderate number of blood vessels. In other areas the membrane was thin, and the two layers could be distinguished only with difficulty and by the use of differential staining methods.

Inferiorly a small cisterna magna could be identified, the wall of which was distinct and separate from the wall of the cyst.

Caudally the cyst membrane was attached to the dorsomedial border of each hemisphere and followed the contour of the cerebellum, without entering into the sulci, to the ventral border, where it bridged the gap between the hemispheres. Rostrally the membrane passed from the vermis laterally and became attached at the dorsolateral border of the cerebellar hemispheres. Ventrally it was affixed to the taenia at the margin of the rhomboid fossa and became continuous with the floor of the fourth ventricle.

The lateral recesses were deep pockets beneath each cerebellar hemisphere, in which small tufts of choroid plexus were seen.

Sections through the cerebral cortex, thalamus and basal ganglia revealed no abnormalities other than slight alterations in the cortical neurons. In some areas the cell processes were stained for long distances. The neurons otherwise seemed normal in staining qualities, and a normal complement of cells was present.

In this case it was clearly demonstrated that there was no fluid communication between the ventricular system and the subarachnoid space. This is not unexpected in view of the pathologic picture. It is noteworthy that no air entered the fourth ventricle, although every means

was used to induce it to do so. Moreover, there was slight but definite dilatation of the aqueduct of Sylvius. The failure of the fourth ventricle to fill must be considered due to a mechanical block of the aqueduct,

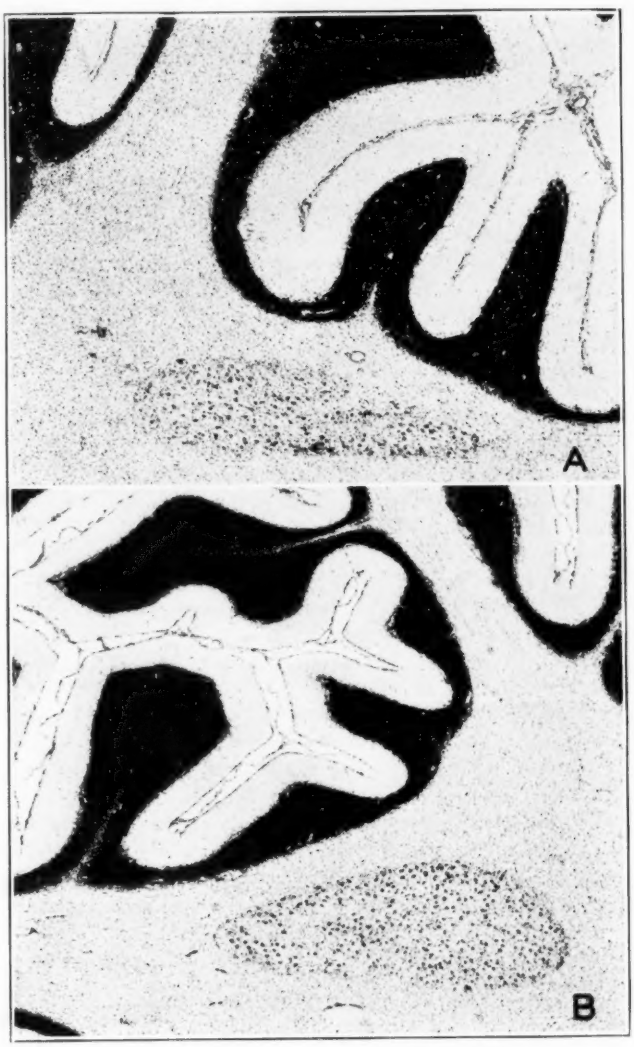

Fig. 9.—Photomicrographs of the heterotopias in the cerebellar white matter resembling the dentate nucleus. *A*, from case 2; *B*, from case 3. Nissl preparation; × 18.

probably the result of compression by the anterior part of the vermis. Such a compression might conceivably occur from sudden relief of pressure above the tentorium, the anterior vermis acting as a valve as the fluid from the fourth ventricle attempted to escape.

COMMENT

That the anomalous conditions in our 3 cases and those in the cases of Dandy and Blackfan, Castrillón, Pines and Surabaschwili, Sahs and Cohen are identical seems indisputable. It is therefore probable that they have a common etiologic factor. If one assumes that the condition represents an agenesis of the posterior part of the vermis, it is difficult to explain the enormous dilatation of the fourth ventricle, which does not occur with primary aplasia of the cerebellar vermis (Rossi [1891], Obersteiner, Lyssenkow and Vogt and Astwazaturow). It seems to us that the primary disturbing factor is absence or delayed opening of the foramens of Luschka and Magendie, which, as stated by Sutton in 1887 (page 360), "must necessarily lead to dilatation of the whole ventricular cavity, and occurring in early embryonic life, hinders the proper development of the cerebellum." It is therefore pertinent to discuss the normal development of the spinal fluid pathways from the fourth ventricle and the embryology of the cerebellum.

Development of the Foramens of Luschka and Magendie.—Weed has studied the development of the fourth ventricle and the subarachnoid spaces about the medulla. After the injection of dyes into the ventricular system in the pig embryo he found no evidence of passage of the foreign matter into the perimedullary tissues until the 15-16 mm. stage. At this period the dye was observed to pass through a localized differentiated area of the rhombic roof. At later stages the dye spread around the medulla, to circumfuse the spinal cord and eventually, at the 24 to 25 mm. stage, to surround the cerebral hemispheres. In the pig the ventricular fluid passed through only the differentiated area, but as the latter became obliterated by the developing cerebellum, a second area formed, through which a functional communication persisted. Although Weed did not follow the development of this second area, it was presumably the beginning of the foramen of Magendie. This opening is not as is sometimes conceived, a punched-out hole in the caudal end of the fourth ventricle, but is a series of larger or smaller holes in the meshwork of fibers formed from the posterior medullary velum (Blake).

The time at which the foramen of Magendie opens has not been definitely established for man. Hess found the foramen patent in a 12 cm. (4 to 5 month) human embryo, and Retzius stated that it was open at the beginning of the fourth month. Kölliker stated that the thinning of the caudal wall of the fourth ventricle, which initiates the process of forming the foramen, begins at the fourth month of embryonic life. It is true that in occasional instances the foramen does not become patent. Retzius found 2 such cases in examining 100 normal adult brains.

The foramens of Luschka are formed by a thinning of the epithelium (Folco) in the lateral recesses of the fourth ventricle; according to Blake, this thinning becomes apparent about the eighth week of fetal life. The foramen is patent at the end of the fourth month (Blake; Hess; Retzius). Karlefors, however, stated that the thinning of the recess wall occurs in the fifth month and the foramen is open at the end of the sixth month.

Occasionally the foramens of Luschka fail to open (Alexander). Retzius found the lateral recesses closed in 5 of 200 hemispheres examined, the atresia being bilateral in 2 cases and unilateral in 1. Hess noted occlusion of the foramen in 5 of 54 brains examined. Karlefors found a somewhat higher incidence, namely, bilateral closure in 4 instances and unilateral closure in 6. On the basis of these data one would expect to find atresia of all three foramens once in about 2,000 brains. Obviously, however, this is incorrect, and the reason is not difficult to understand. When all three foramens are atresic, the endoventricular pressure will increase and thus stimulate thinning of the posterior medullary velum at the sites of the foramens, but if only two are closed, the endoventricular pressure may remain normal, the condition thus not favoring an opening of the other foramen.

It is, then, apparent that a fluid communication exists between the fourth ventricle and the perimedullary tissues before the formation of the foramens of Luschka and Magendie (Weed [1932]). It is the presence of this fluid which apparently initiates the formation of the subarachnoid space. It is, then, understandable that complete atresia of the foramens of Luschka and Magendie may be present when the basal cisterns and subarachnoid space are normal.

Development of the Cerebellum.—By the fourth week of intrauterine life the neural tube has closed, the neuropores are no longer seen and the prosencephalon, mesencephalon and rhombencephalon may be distinguished (Gray). From the rhombencephalon the medulla oblongata, pons Varolii and cerebellum develop. At the fourth week cellular differentiation in the pontile region has resulted in the development of a prominent flexure and a corresponding fissure, with thinning of the roof plate. This fissuration results in the division of the rhombencephalon into the metencephalon and the myelencephalon. The metencephalon is the primordium of the cerebellum.

As a result of thickening, the lateral plates of the metencephalon project into the fourth ventricle at the sixth week, forming the cerebellar commissure, which is the primordium of the anterior vermis. At the third month these projections unite in the midline at their cephalic borders (Ingvar). From this point until the fifth month the vermis

increases rapidly in size. At the same time the marginal cells of the vermis and the hemispheres proliferate more rapidly than the underlying tissues, resulting in the formation of the fissures and folia of the developed cerebellum.

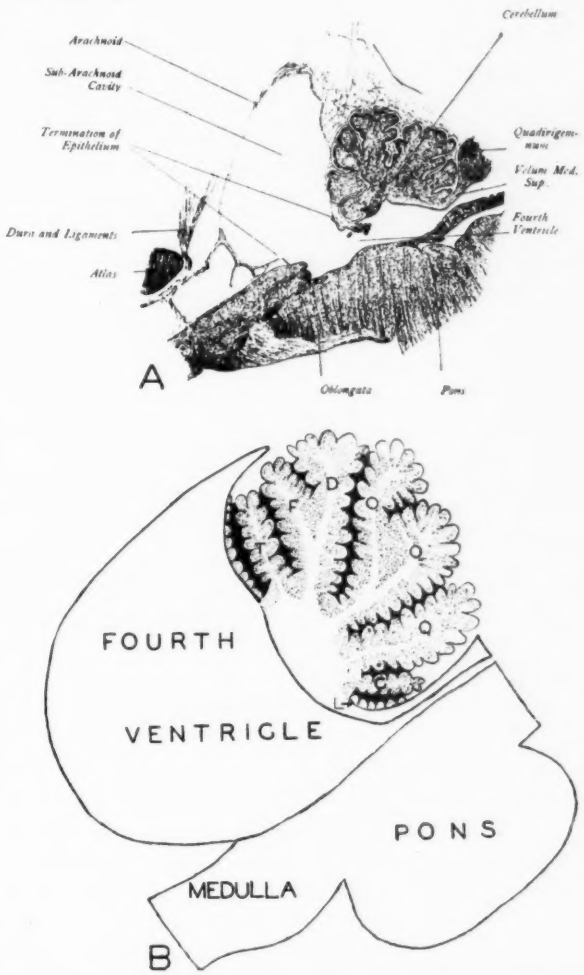

Fig. 10.—*A*, drawing from Blake, showing the development of the cerebellar vermis, the fourth ventricle and the subarachnoid space at the fourth month of intrauterine life.

B, sketch of the cerebellar vermis and the dilated fourth ventricle in case 3. The similarity of the development of the cerebellum in these two illustrations is striking. The large cystlike structure which Blake represents and labels "sub-arachnoid cavity" is a normal feature of the developing basal cisterns, according to Dr. R. M. Strong (personal communication). This structure appears to form the cisterna magna. The divisions of the cerebellar vermis are indicated (*C* is lobulus centralis; *D*, declivis; *F*, folium; *L*, lingula; *O*, culmen, and *T*, tuber).

The formation of the anterior and the posterior vermis does not proceed coincidentally, however (Dow). After the union of the lateral plates in the midline the lateral commissure appears slightly caudal to the cerebellar commissure. At a later stage cells migrate along the lateral commissure to form the anlage of the flocculonodular lobe (Larsell). The fusion of these elements to form the nodulus occurs later than the fusion of the structures about the cerebellar commissure. The posterior vermis thus is the last to develop. Then, if the evolution of the cerebellum is arrested during its differentiation, the anterior lobe and the hemispheres would be well formed, while the structures of the posterior vermis would be absent or vestigial (fig. 10).

PATHOGENESIS OF CONGENITAL ATRESIA OF THE FORAMENS OF LUSCHKA AND MAGENDIE

The development of the cerebellum at the end of the fourth month of fetal life is such that failure of the foramens of Luschka and Magendie to open normally would preclude the differentiation of the posterior part of the vermis, owing to separation of the parts of the lateral commissure as a result of the enlargement of the fourth ventricle. If the opening is only delayed the dilatation of the fourth ventricle (hydrocele) remains but progressive hydrocephalus will not develop. Such a condition presumably prevailed in the cases reported by Castrillón, Pines and Surabaschwili and Sahs, in which the foramens of Luschka and Magendie were patent at autopsy. But even in these cases the transient intracranial hypertension and hydrocephalus at an early stage of fetal life probably had a deleterious effect on the development of the cerebral cortex. It is, hence, not surprising that in certain of these cases there was mental deficiency.

The question may be asked whether complete atresia of the foramens of Luschka and Magendie is possible without the production of severe progressive hydrocephalus, which would shortly be incompatible with life. We believe that several factors operate in cases of this anomaly to produce a balance of cerebrospinal fluid dynamic pressures. Certainly, the abnormally small choroid plexuses produce less ventricular fluid than normal. Again, the cyst wall probably acts as a semipermeable membrane permitting dialysis of the ventricular fluid, which has a lower osmotic pressure than cerebrospinal fluid in the basal cisterns and the subarachnoid space. A third factor is the absorption of some fluid by the numerous vessels in the cyst wall itself. These compensating mechanisms probably have little reserve, so that a slight disturbance of any one of them might precipitate a state of intracranial hypertension. It is reasonable to suppose that in those cases in which

the foramens open late or inadequately development may be normal until some extrinsic factor upsets the delicate balance of the cerebrospinal fluid dynamic pressure. The "neck-strengthening" exercises in Sahs's case would seem to be such a precipitating factor. On the other hand, in those cases in which there is complete atresia of the foramens one might expect earlier and more fulminant symptoms and signs.

CLINICAL ASPECTS OF CONGENITAL ATRESIA OF THE FORAMENS OF LUSCHKA AND MAGENDIE

From this small series it is impossible to describe a typical case of the disease, nor are generalizations possible. There does not appear, however, to be a predilection as to sex, for of the 8 patients whose sex was given, 4 were males and 4 females. The age incidence appears to be significant, for half the patients were about 1 year old. Enlargement of the head, with or without symptoms of intracranial hypertension, is the most common presenting complaint. It is noteworthy that both the adults were mentally retarded; possibly the children would have been found similarly defective if adequate testing had been possible. Examination reveals nothing outstanding other than the enlargement of the head. Papilledema is present in half the cases. Cerebellar signs are not pronounced. In the infants there is little to distinguish the condition from communicating hydrocephalus except for the unusually large occipital region of the head and the roentgenologic signs, which are practically pathognomonic of the condition.

ROENTGENOLOGIC ASPECTS OF CONGENITAL ATRESIA OF FORAMENS OF LUSCHKA AND MAGENDIE

The gross alterations in the nervous system produced by this anomaly are reflected in the osseous coverings of the brain (fig. 11). The roentgenologic changes in the skull in the 3 cases reported are identical. To understand the genesis of these osseous abnormalities it is necessary to review the embryology of the skull and the venous channels of the head.

Once the brain has been enclosed by the membranous cranium, the skull develops quite independently of the nerve tissue (Gray). Its primary centers of ossification, which determine its evolution, are laid down at a time when the brain is in a primitive form. Centers of ossification appear in both the parietal and the occipital bone at about the second month of fetal life. The planum occipitale (that portion of the squama occipitalis which lies above the highest nuchal line) has four centers of ossification, two near the midline, appearing about the second month, and two slightly more laterally placed, developing at

the third month of fetal life. The planum nuchale (the portion of the squama occipitalis which lies below the supreme nuchal line) is ossified from two centers, which appear about the seventh week of fetal life and soon unite. Osseous union of the upper and the lower part of the squama occurs about the third month. The parietal bone has one central point of ossification, which appears at about the second month of intrauterine life. Such early ossification allows the evolution of the cranium to proceed independently of the enclosed nerve tissue.

The venous sinuses, on the contrary, are dependent to a considerable extent on the development of the brain (Streeter). We are concerned with the sagittal and lateral sinuses, which are derivatives of the anterior venous plexus of the dura. These channels, originally

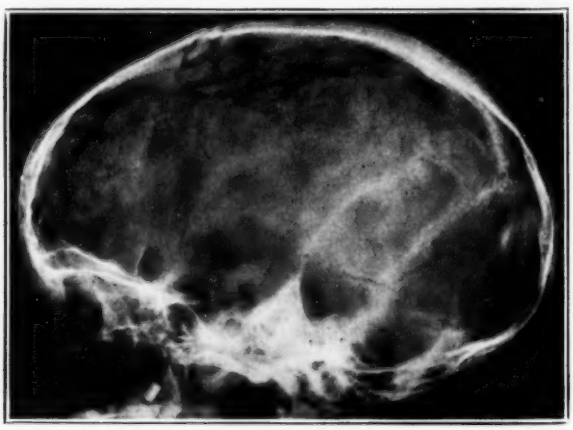

Fig. 11 (case of Cohen).—Typical and pathognomonic roentgenologic appearance of the skull associated with congenital atresia of the foramens of Luschka and Magendie. Note the position of the lateral sinus on the parietal bone and the enormous posterior fossa. (This roentgenogram is reproduced by permission of Dr. Ira Cohen, who loaned us the original film).

lying on the anterior surface of the telencephalon, become displaced posteriorly as the cerebral hemispheres fold backward. This is accomplished by traction on the vessels (passive migration) and, at the same time, by diversion of the main stream to more posterior loops of the venous plexus (spontaneous migration). By this means the anterior venous plexus has formed at the third month of fetal life a confluent sinus (torcular Herophili), which lies in the midline just above the superior margin of the squama occipitalis. Entering into this sinus is the superior sagittal sinus, and leaving it are the lateral,

or transverse, sinuses, which lie on the parietal bones. Under normal circumstances the confluent and transverse sinuses migrate posteriorly in the latter part of fetal life until they reach their normal position on the occipital bone (fig. 12).

Consider, however, the condition which develops if the foramens of Luschka and Magendie fail to open. The fourth ventricle, enlarging to fill the greater part of the posterior fossa, tends to prevent the

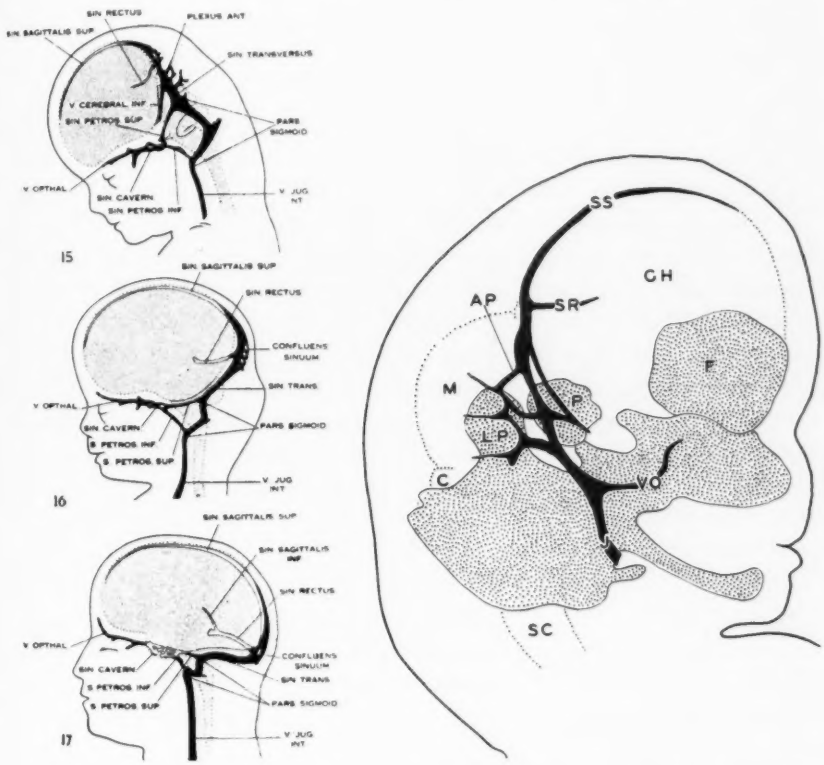

Fig. 12.—At the left is a series of diagrams by Streeter, showing the evolution of the lateral sinuses; *15*, the sinuses of a 10 week embryo; *16*, the sinuses of a 3 month embryo, and *17*, the sinuses of an adult. At the right is a composite illustration, showing the skull bones and the sinuses at the fetal age of approximately 10 weeks. The abbreviations used in this illustration are as follows: *AP*, plexus anterior; *C*, cerebellum; *CH*, hemisphaerium cerebrale; *F*, os frontale; *J*, vena jugularis; *LP*, os occipitale, pars lateralis; *M*, mesencephalon; *P*, os parietale; *SC*, medulla spinalis; *SR*, sinus rectus; *SS*, sinus sagittalis superior, and *VO*, vena ophthalmica.

posterior migration of the transverse and confluent sinuses. They therefore retain their fetal position, and their impression becomes molded on the inferior part of the parietal bone (Macklin).

The significance of this abnormal position of the lateral sinus and the torcular Herophili has only recently been recognized. Bucy, who saw our first 2 cases, described the roentgenologic picture and credited Dandy with first demonstrating it. Since the anomaly can be produced only by lesions which occur early in fetal life and since inflammations and neoplasms, which are the other common causes of occlusion of the foramens of Luschka and Magendie, practically never occur at that age without producing a condition incompatible with life, the aforedescribed roentgenologic picture may be considered practically pathognomonic of congenital atresia of the foramens of Luschka and Magendie.

TREATMENT

The results of surgical treatment of this condition have not been encouraging. Seven patients were subjected to some form of surgery. Of these, 4 succumbed very shortly after operation. One child died one month after ventricular puncture. Only 2 patients have survived, those of Scarff and Cohen. It is interesting that in both cases as much of the membrane was removed as seemed feasible. Third and fourth ventriculostomies have been done, without success. One of our patients died shortly after ventriculography. Although all of these procedures result in severe disturbances of the cerebrospinal fluid dynamics, which may cause death through subependymal hemorrhage and cerebral edema, it is possible that other abnormalities in the brain stem or hypothalamus may be responsible.

The method of choice in the treatment of patients with this anomaly is, of course, not established. It would seem wise to try conservative measures, such as dehydration and ventricular puncture, with or without continuous ventricular drainage, to tide the patient over an acute episode. In the event of a continued unfavorable course, the posterior fossa should be explored and the membrane excised as widely as possible.

SUMMARY

Three cases of congenital atresia of the foramens of Luschka and Magendie are presented in detail. The pathogenesis of the enormous dilatation of the fourth ventricle and the lack of development of the posterior part of the vermis are explained on an embryologic basis.

The clinical picture of the condition is not typical, although most of the cases occur in infancy or childhood and in many the condition is probably diagnosed as noncommunicating hydrocephalus.

The roentgenologic findings are, however, practically pathognomonic of the condition. The impression of the confluent and lateral sinuses

is on the parietal bone. The normal posterior migration of the sinuses with the development of the cerebral hemispheres is interfered with by the dilated fourth ventricle.

The treatment is not satisfactory; surgical removal of the cyst membrane has been successful in 2 cases.

University of Chicago.

DISCUSSION

DR. R. M. STRONG, Chicago: This paper interests me greatly because the existence of the foramens of Luschka and Magendie has been of research interest for the past fifteen years, during which time I have had several students working on the problem. Although the textbooks and many authors state that there are such apertures in the human fourth ventricle, there are still those who do not agree.

At the meeting of the American Association of Anatomists in Toronto, five years ago, I read a paper presenting evidence of the existence of the foramen of Magendie. In the discussion which followed, Ariens Kappers stated that dissections of adult human brains in his laboratory did not support the existence of this foramen. I believe, however, that it does exist.

During this winter I have resumed work on the problem. There is a structure in apparently normal human embryos, at stages representing the early development of the cerebellum, which, if it should persist and enlarge, could become the cyst Dr. Taggart has described.

DR. JOHN K. TAGGART JR., Chicago: We believe that the roentgenographic picture is pathognomonic of this condition, and we feel that the condition can be diagnosed without exploration of the posterior fossa.

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BOECK'S DISEASE (SARCOID) OF THE CENTRAL NERVOUS SYSTEM

REPORT OF A CASE, WITH COMPLETE CLINICAL AND PATHOLOGIC STUDY

T. C. ERICKSON, M.D.
MADISON, WIS.
AND
G. ODOM, M.D.
AND
K. STERN, M.D.
MONTREAL, CANADA

The following case is of interest for two reasons. First, there was present the clinical picture of adhesive arachnoiditis of obscure origin. Second, the paucity of pathologic studies on Boeck's sarcoid in the central nervous system makes the observations on this patient of especial importance.

REPORT OF CASE

History.—A French Canadian aged 31, the operator of a small printing press, was admitted with the chief complaint of diminished visual acuity, beginning in June 1940, recurring attacks of dizziness of increasing frequency and suboccipital headaches, radiating to the frontal region. He stated that before the onset of these symptoms he had considered himself in good health, but added that he had had a nodular lesion on his upper lip (fig. 1) since February 1940. Further questioning revealed that he had had diminution of auditory acuity and tinnitus in the left ear for three months, projectile vomiting, inability to think clearly and loss of weight from 220 to 185 pounds (99.8 to 83 Kg.).

Examination.—The following abnormal conditions were demonstrated: (1) pronounced bilateral papilledema with retinal hemorrhages; (2) slight mental dulness and apathy; (3) obesity, with recent loss of weight and a basal metabolic rate of —19.6 per cent, and (4) a dry, crusted lesion, 2 cm. in diameter, with elevated nodular border on the upper lip (fig. 1). The Wassermann reactions of the blood and spinal fluid were negative; the results of urinalysis were normal, as was the dextrose tolerance curve. The electroencephalogram showed random and rhythmic delta waves, which were not clearly localized.

Because of the rapidly advancing papilledema and visual loss, a ventriculogram was made. This revealed symmetric dilatation of the lateral, third and fourth ventricles. A provisional diagnosis of adhesive arachnoiditis and obstruction of the foramens of Luschka and Magendie was made, and on Sept. 13 a myoplastic suboccipital craniotomy was performed by one of us (T. C. E.).

Operation.—There was a herniation of the tonsillar lobes of the cerebellum through the foramen magnum down to the level of the arch of the atlas. The left tonsillar lobe was twice the size of the right, and both were adherent to

From the Montreal Neurological Institute.

the surrounding dura. Their surface was covered with thickened, tough, whitish pia-arachnoid. In order to relieve the block in the cerebrospinal fluid circulation, the major portion of the left tonsillar lobe of the cerebellum was amputated.

Postoperative Course.—Recovery was uneventful except for persistent hiccups, which ceased spontaneously, and a small cerebrospinal fluid leak from one trepanation opening, which also ceased sixteen days after operation. The papilledema receded rapidly and was completely absent on his discharge from the hospital on October 18. Lumbar puncture, however, revealed that the spinal fluid proteins were elevated to 372 mg. per hundred cubic centimeters. The spinal fluid was clear, pale and straw colored, with only 3 mononuclear cells per cubic millimeter and a pressure of 175 mm. when the patient was in the recumbent position. Spinal fluid culture showed no aerobic or anaerobic growth. Guinea pigs inoculated with the spinal fluid showed no evidence of tuberculosis. The intradermal tuberculin test (0.01 mg.) was negative, although a roentgenogram of the chest revealing infiltration in the upper and lower portions of the left lung and the lower field of the right lung had been interpreted as evidence of minimal bilateral active pulmonary tuberculosis.

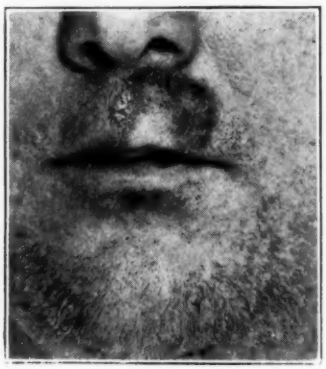

Fig. 1.—Photograph of the chronic lesion of the upper lip, which had been present for a year before death.

A roentgenogram showed a normal appearance of the bones of the hands and feet, with none of the small punched-out areas in the phalanges characteristic of Boeck's sarcoid.

The patient was seen in consultation by Dr. F. Cormia, who expressed the opinion that the lesions of the lip and the cerebellum might both be syphilitic, in spite of the negative Wassermann reactions of the blood and spinal fluid. A therapeutic test with daily mercury rubs for fifteen days produced no improvement in the ulcer on his lip. In fact, this lesion increased in size, while there was no influence on the other symptoms.

Subsequent Hospitalizations.—The patient was hospitalized in the Montreal Neurological Institute a second time from Dec. 16 to 20, 1940 for further study. At this time he said that his vision was greatly improved and that the headache and vomiting had disappeared. He continued to have dizzy spells, however, and there had been a gradual increase in size of the lesion on the upper lip. Examination revealed that the craniotomy wound was well healed but that there had been a decided increase in the obesity, with relative atrophy of the lower extremities.

He was admitted a third time on Feb. 18, 1941 because of recurrence of the headache, nausea and vomiting, progressive loss of vision, ataxia and a further gain of 30 pounds (13.6 Kg.) in weight, which occurred rather acutely a month before. Examination revealed an increase in size of the lesion of the upper lip, which was described as a crescent-shaped series of nodules extending from the nose to the mucous membrane of the upper lip (fig. 1). There was also a recurrence of the papilledema, with decreased visual acuity, pronounced nystagmus, slight loss of hearing bilaterally, marked ataxia, generalized muscular weakness and increased deep reflexes on the left. The patient showed a decided increase in his obesity, and there was a female distribution of the fat and hair.

The results of chemical studies on the blood, done on March 15, were as follows: total protein nitrogen 1,060 mg. per hundred cubic centimeters (serum protein 6.62 Gm. per hundred cubic centimeters), albumin nitrogen 666 mg. per hundred cubic centimeters (albumin 4.16 Gm. per hundred cubic centimeters) and globulin nitrogen 394 mg. per hundred cubic centimeters (globulin 2.46 Gm. per hundred cubic centimeters); phosphatase 15.4 Bodansky units, and bilirubin, indirect reaction, 0.04 mg. per hundred cubic centimeters. Morphologic examination of the blood gave normal results except for leukocytosis (white cell count 11,900), due to an increase of polymorphonuclear cells with reduction of monocytes and lymphocytes. There was no eosinophilia. The sedimentation velocity was normal. On repetition the Wassermann reactions of the blood and spinal fluid were again negative. The spinal fluid was under increased pressure (370 mm. of water, with the patient in the horizontal position) and contained 261 mg. of proteins per hundred cubic centimeters and 50 lymphocytes per cubic millimeter. The rectal temperature was consistently normal, and the blood pressure was 120 mm. of mercury systolic and 76 mm. diastolic.

With a diagnosis of Boeck's sarcoid, confirmed by biopsy of tissue from the cerebellum and the lesion of the lip, the patient was given a series of roentgen treatments (6,000 r). During this time there was definite improvement of the lesion on the lip, but not of his other symptoms. He began to have sudden attacks of loss of consciousness, suggesting ictus infratentorialis, similar to the attack before his operation. On March 25, 1941, five days after completion of roentgen therapy, the patient had such an attack and died with respiratory failure.

Autopsy.—Examination revealed firm adhesions over the cerebellum and the inferior surface of the occipital lobes. There was considerable ironing out of convolutions over both hemispheres, but no asymmetry and no midline shift of the base or vertex. Adhesions and a plastic exudate covered the structures of the base. Over the posterior surface of the brain stem, and extending between it and the foramen magnum, was a moderate amount of grayish fibrous hemorrhagic tissue. On gross inspection the cord appeared normal. The weight of the brain was 1,375 Gm. The formaldehyde-fixed brain was cut in coronal sections. All the ventricle walls were covered with glistening granules 0.5 to 1 mm. in diameter. There was no other gross evidence of parenchymatous lesions of the brain.

Blocks of tissue were embedded in paraffin and studied by means of the following stains: hematoxylin and Van Gieson, phosphotungstic acid hematoxylin, the Nissl and Loyez technics, the Penfield stain for oligodendroglia, the Hortega stain for microglia, the Globus-Cajal method for astrocytes, scarlet red and the Spielmeyer and Ziehl-Neelsen methods.

Microscopic Study.—The pituitary showed a few clusters of epithelioid cells in its capsule, with an occasional multinucleated giant cell. In the pia-arachnoid over the pons, mesencephalon and cerebellum there were nodules consisting of round cells, plasma cells, epithelioid cells and giant cells (fig. 2 *A*). All these

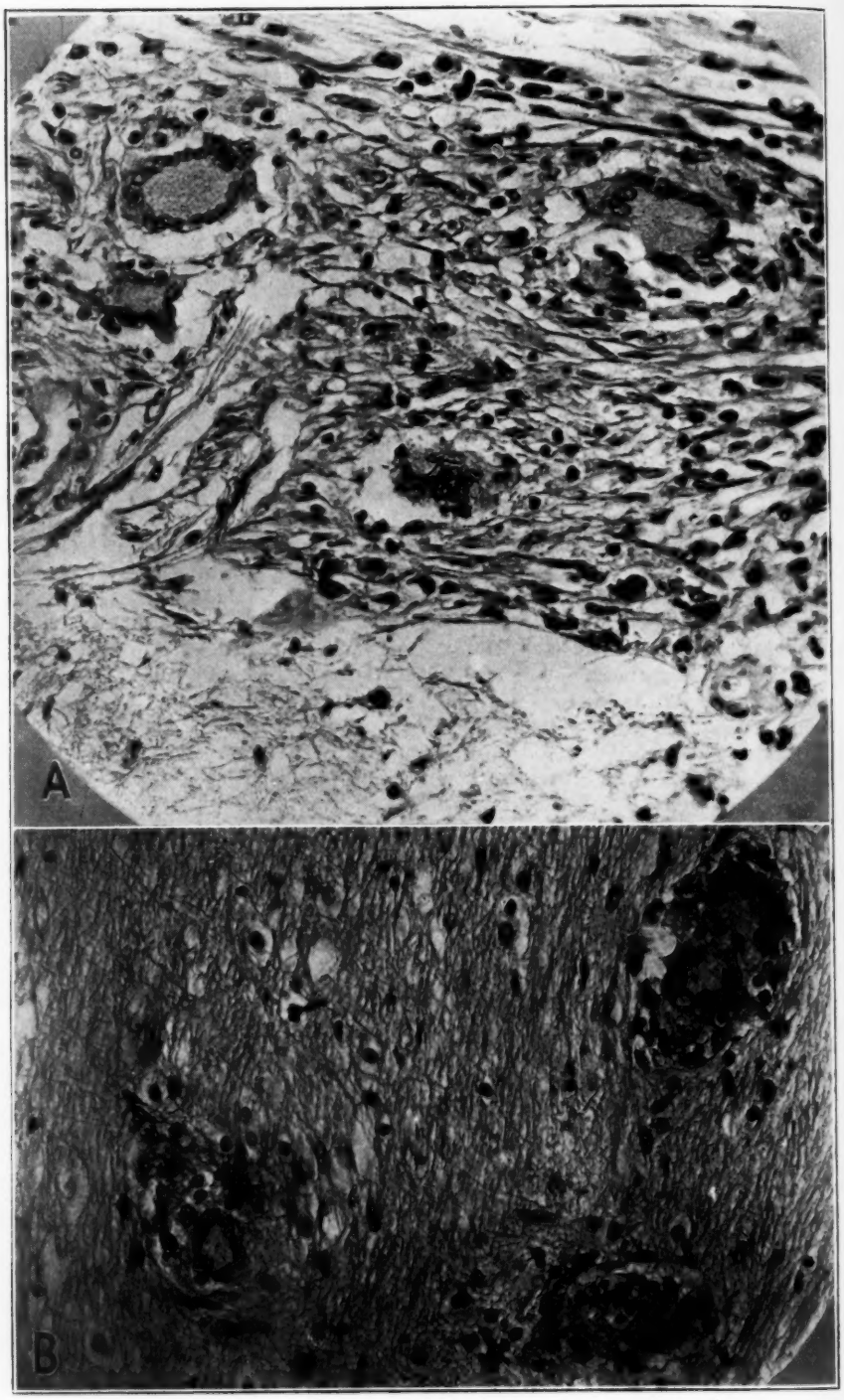

Figure 2

(See legend on opposite page)

cells appeared to be suspended in a connective tissue reticulum, which contained a good deal of collagen. In one of the nodules the connective tissue produced a capsule. In the immediate neighborhood of these areas the meninges were more diffusely infiltrated with round cells and macrophages, but large parts of the meninges were completely free. These areas had a tendency to be in the neighborhood of larger vessels. They could be seen over the cerebellum as well as the pons. The nerve roots were free. Within the nerve substance of the pons and cerebellum, some small vessels showed collections of plasma cells, round cells and epithelioid cells, with occasionally a giant cell in the perivascular spaces (fig. 2 *B*). Similar changes were observed in the cerebellopontile angle.

Changes in the medulla were most noticeable. The lateral recess and part of the tela choroidea of the fourth ventricle were occupied by huge conglomerations of tissue similar to that in the smaller foci previously described. Giant cells were scattered throughout these areas irregularly. There was marked proliferation of connective tissue with reticulum formation, in which numerous round cells, plasma cells and epithelioid cells were suspended. Here, again, the tendency to necrosis was minimal. The masses also appeared to occupy the stalk and part of the choroid plexus. Smaller foci, similar to the ones already described, were scattered over the pia-arachnoid of the cerebellum and over the base of the pyramid on one side. In the last-mentioned focus the formation of collagen in the recticulum was particularly rich. One of the small foci was round and showed in its center a slit containing red blood cells and lined with endothelium, so that it appeared that a complete vessel wall was occupied by this granulomatous tissue. The arteries were well intact, even within the most severely involved areas. Within the nerve substance itself were perivascular infiltrations similar to the ones described in previous sections, especially in the subependymal layer. Deep in the nerve substance, one could see small vessels with a giant cell and a very few round cells attached to them. Single giant cells with one or two lymphocytes could also be seen free in the nerve tissue, apparently without demonstrable attachment to a vessel. The nerve cells were well preserved. There was a mild diffuse increase of astrocytes.

The meningeal changes over the infundibulum, mammillary bodies, peduncles and optic tracts consisted of circumscribed foci similar to those observed in the midbrain. The changes within the nerve substance resembled the ones previously described. The connective tissue surrounding the pituitary stalk was completely occupied by granulomas. There were several small ones in the paraventricular nucleus, the substantia innominata and the optic chiasm. A solid, well circumscribed granulomatous area lay within the stroma and stalk of the choroid plexus of the right ventricle. A few small granulomas were present in the subependymal zone.

The area of adhesions between the brain stem and the foramen magnum consisted of dense connective tissue rich in collagen. At one end of the section there were a few foci similar to the ones described in the pia-arachnoid.

EXPLANATION OF FIGURE 2

A, hematoxylin–Van Gieson stain of a section from the meninges over the cerebellum, showing a typical nodule consisting of small round cells, epithelioid cells, plasma cells and giant cells. *B*, hematoxylin–Van Gieson stain of a section through the pons, showing isolated foci of giant cells.

The cervical, thoracic and lumbar regions of the spinal cord were observed to contain patchy infiltrations of a similar nature, but much less intense than those in the brain stem.

The meninges over the frontal cortex showed moderate infiltration with macrophages, round cells, plasma cells and epithelioid cells. No giant cells were seen, and there was no tendency toward necrosis. The cortex itself showed no changes apart from slight superficial gliosis. Mild meningeal infiltration appeared in one area of the motor cortex. A few small intracerebral vessels showed a mild degree of cuffing. Similar changes were noted in the visual cortex.

Permission for a complete postmortem examination was not obtained; therefore only several pieces of lung were obtained. They showed most of the lung tissue to be replaced by large caseous areas surrounded by lymphocytes, plasma cells, epithelioid cells and Langhans' giant cells.

COMMENT

The differential diagnosis in this case lay between a syphilitic or tuberculous lesion, on the one hand, and Boeck's sarcoid, on the other. The repeated negative Wassermann reactions of the blood and spinal fluid, as well as the lack of therapeutic response to antisyphilitic treatment, rules out syphilis as the causative factor. Tuberculosis would seem to be eliminated as a cause of the lesions in the central nervous system because of the failure to detect tuberculosis in guinea pigs inoculated with spinal fluid. Intradermal tuberculin tests were also negative, and no tubercle bacilli could be stained in the biopsy tissue taken from the cerebellum or the lesion of the lip. Histologic study of biopsy material from the posterior fossa, however, showed an identical granulomatous process in the cerebellar tissue and the biopsy specimen from the upper lip.

The histopathologic changes in the nerve parenchyma and meninges, as well as in the lip, were typical of those described for Boeck's sarcoid, i.e., multiple granulomas of epithelial cells, giant cells, round cells and plasma cells, with no inflammatory reaction and conspicuously little tendency to necrosis or caseation. Even from a purely morphologic point of view these lesions are atypical either of tuberculosis or of syphilis. Tuberculous meningitis with such a decided tendency to the formation of circumscribed tubercles and with such little tendency to necrosis is in itself extraordinary. The so-called miliary gummas of the meninges and brain, as described by Jakob,[1] also differ widely from the lesions which have been described.

The phosphatase in our patient was elevated, a frequent observation in cases of Boeck's sarcoid, but of course not pathognomonic. Hyperproteinemia and hyperglobulinemia, although common in sarcoidosis, disappear as the lesions heal. In our patient the total serum protein

1. Jakob, A.: Die Syphilis des Gehirns und seiner Häute, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, p. 349.

of 6.62 Gm., while not elevated, is in keeping with values reported in some of the other proved cases of Boeck's sarcoid (Harrell and Fisher [2]).

The etiology of Boeck's sarcoid is obscure, but many authorities have called it a peculiar form of tuberculosis. The literature has been well reviewed by Longcope and Pierson [3] and by Hannesson.[4] In the great majority of reported cases the intradermal tuberculin tests have been negative, as they were in our case. On the other hand, coexisting pulmonary tuberculosis has been noted in about 10 per cent of the reported cases.

This patient first presented a problem of acute increase of intracranial pressure due to obstruction of the outflow of cerebrospinal fluid through the foramens of Luschka and Magendie. This block was effectively relieved by suboccipital craniotomy, with amputation of the left cerebellar tonsil and lysis of adhesions. This improvement lasted four months, only to recur. The recurrent involvement in the central nervous system did not respond favorably to roentgen therapy, and, in retrospect, more radical surgical therapy would have been the procedure of choice to tide the patient over the period of increased intracranial pressure.

To the neurosurgeon, in particular, the gross appearance of the lesions observed at operation and the ventriculographic changes are of interest because they suggested adhesive arachnoiditis. In view of the obscure nature of most cases of arachnoiditis, this raises the question whether ephemeral lesions of Boeck's sarcoid may not be the responsible factor in the occasional case of adhesive arachnoiditis. More biopsies in cases of adhesive arachnoiditis might serve to clear up this point. Moreover, the sarcoid lesion may undergo complete replacement by fibrous tissue, so that there remains no histologic evidence of the preceding granuloma (Palmer [5]).

Although Boeck's sarcoid is disseminated widely in the body, involvement of the nervous system seems to be uncommon. None of the patients studied by Longcope and Pierson [3] presented signs or symptoms indicating disease of the central nervous system.[6] Because of its usually

2. Harrell, G. T., and Fisher, S.: Blood Chemical Changes in Boeck's Sarcoid with Particular Reference to Protein, Calcium and Phosphatase Values, J. Clin. Investigation **18**:687-693, 1939.

3. Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), Bull. Johns Hopkins Hosp. **60**:223-296, 1937.

4. Hannesson, H.: Besnier-Boeck's Disease: A Review, Brit. J. Tuberc. **35**:88-113, 1941.

5. Palmer, J. H.: Boeck's Disease (Sarcoid): Its Clinical Groups and Diagnosis, Canad. M. A. J. **43**:11-18, 1940.

6. In a recent article W. T. Longcope, (Sarcoidosis, J. A. M. A. **117**:1321-1327 [Oct. 18] 1941) described involvement of the meninges in 2 cases, of the cervical portion of the cord in 1 case, of the pituitary in 1 case and of the hypothalamus in 1 case.

benign chronic course, knowledge of the pathologic change in the central nervous system is scant. We have found only 2 cases with reports of histologic study of the nervous system.[7] Bang,[8] in a case of uveoparotid fever and convulsions, observed multiple "tuberculomata" in the cerebrum, cerebellum and pons. Reis and Rothfeld[9] reported a case of sarcoid terminating with convulsive seizures in a girl of 17 who showed changes in the skin and bones. At autopsy, a tumor-like mass composed of tissue typical histologically of sarcoid was seen on the optic nerve. The same case was apparently recorded by Lenartowicz and Rothfeld.[10]

Diabetes insipidus has been reported in cases of sarcoidosis (Hannesson[4]). There are also records of sarcoid lesions in the hypophysis (Schaumann[11]). Paralysis of the facial nerve is said to accompany the swelling of the parotid glands in about one-half the patients with uveoparotid fever (Garland and Thompson[12]), a syndrome which is now generally considered as a distinctive form of sarcoid. Levin[13] reviewed the neurologic manifestations of uveoparotid fever. In our patient there was no indication that disease of the parotid gland or the uveal structures had preceded the meningeal or cerebellar involvement. Neither was there any peripheral lesion of the facial nerves.

SUMMARY

Sarcoid of the central nervous system has been recognized with extreme rarity. Our case presented a clinical picture of adhesive arachnoiditis with internal hydrocephalus, due to blockage of the cerebrospinal fluid pathways about the foramen magnum. Suboccipital craniotomy revealed herniation of the tonsillar lobes of the cerebellum, with dense arachnoid adhesions. Biopsy specimens from the cerebellum and arach-

7. Two additional cases were reported by Sands and Riley at the Sixty-Eighth Meeting of the American Neurological Association on June 4, 1942.

8. Bang, S.: Febris Uveo-Parotidea, Ugesk. f. læger **80**:571-588, 1918; cited by Levin.[13]

9. Reis, W., and Rothfeld, J.: Tuberkulide des Sehnerven als Komplikation von Hautsarkoiden vom Typus Darier-Roussy, Arch. f. Ophth. **126**: 357-366, 1931.

10. Lenartowicz, J., and Rothfeld, P.: Ein Fall von Hautsarkoiden (Darier-Roussy) mit identischen Veränderungen im Gehirn und den inneren Organen, Arch. f. Dermat. u. Syph. **161**:504-519, 1930.

11. Schaumann, J.: Lymphogranulomatosis Benigna in the Light of Prolonged Clinical Observations and Autopsy Fndings, Brit. J. Dermat. **48**: 399-446, 1936.

12. Garland, H. G., and Thompson, J. G.: Uveo-Parotid Tuberculosis (Febris Uveo-Parotidea of Heerfordt), Quart. J. Med. **2**:157-177, 1933.

13. Levin, P. M.: The Neurological Aspects of Uveo-Parotid Fever, J. Nerv. & Ment. Dis. **81**:176-191, 1935.

noid showed a granulomatous process identical with that in specimens taken from a nodular lesion of the upper lip, and a diagnosis of Boeck's sarcoid was thus established during life. The patient died shortly after receiving a series of high voltage roentgen ray treatments six months after operation.

Postmortem examination showed adhesions and exudate over the base of the brain and over the dorsal aspect of the lower portion of the brain stem. Microscopically there was meningoencephalitis, characterized by isolated and conglomerated foci made up of numerous epithelioid cells, giant cells, round cells and plasma cells. Similar lesions, but with more tendency to necrosis, were observed in the lung.

State of Wisconsin General Hospital, Madison, Wis.

Montreal Neurological Institute.

Montreal Neurological Institute.

VIBRATORY SENSIBILITY

A QUANTITATIVE STUDY OF ITS THRESHOLDS IN NERVOUS DISORDERS

JAMES C. FOX JR., M.D.
AND
WOLFGANG W. KLEMPERER, M.D.
NEW HAVEN, CONN.

HISTORICAL BACKGROUND

Vibratory sensation, both the exploration of its nature and its clinical interpretation, has intrigued physiologists, neurologists, otologists and psychologists for the past one hundred years. Johannes Mueller,[1] in 1830, mentioned it briefly in his textbook of physiology, to adduce further evidence for his doctrine of the "specific energy of nerves." The first to analyze this sensation was Weber,[2] who, in his admirable monograph on sensation (1842), wrote in the chapter on the relationship of the sense of feeling to other senses:

> In the rapidly successive impulses falling on sensory end organs one has a transition from feeling to hearing. By their confluence, these impulses make up a sensation, which can be altered by the length of the intervals between them. These vibrations are felt as a movement, which is taken up by the auditory apparatus as a tone. It is subject to manifold modifications, such as, for instance, the sensation one has, when skating, in changing from rough to smooth ice.

Valentin[3] (1852) studied the influence of extrinsic factors on vibratory perception with an instrument of his own invention. This was a cogwheel driven at known speed, enabling him to determine interrupted impulses of the highest frequency that were still perceptible as vibration.

From the Department of Internal Medicine, Yale University School of Medicine.

Read at the Sixty-Seventh Annual Meeting of the American Neurological Association, June 11, 1941, Atlantic City, N. J.

Dr. Fox and Dr. Klemperer are now serving with the Medical Corps of the United States Army. Dr. Fox at present is stationed at Camp Edwards, Mass., and Dr. Klemperer, at Fort Dix, N. J.

1. Mueller, J.: Elements of Physiology, translated by W. Baly, London. Taylor and Walton, vol. 2, book 5.

2. Weber, E. H.: Tastsinn und Gemeingefühl, in Wagner, R.: Handwörterbuch der Physiologie, Brunswick, F. Vieweg u. Sohn, 1842, vol. 3, p. 401; reprinted in Ostwald, W.: Klassiker der exacten Wissenschaften, Leipzig, W. Engelmann, 1905, no. 5.

3. Valentin, G.: Ueber die Dauer der Tasteindrücke, Arch. f. physiol. Heilk. **11**:438 and 587, 1852.

Before experimenting he would also dip his fingers into water, acids or ether, expose them to heat or cold or decrease their blood supply with a tourniquet, and he found that all these factors lessened vibratory perception. Even more remarkable were the experiments of von Wittich,[4] who in 1869 used monochords, organ pipes and disks, as well as cogwheels to produce vibratory stimuli. At the end of his paper Valentin [3] pointed to the possible value of such studies in the field of clinical medicine, but it was not until about twenty years later (1889) that Rumpf [5] introduced the tuning fork. He used fourteen different forks, with vibratory rates from 13 to 1000, explored the normal vibratory thresholds and compared them with the abnormal values in a case of syringomyelia.

The tuning fork was modified for auditory tests first by Gradenigo [6] in 1899 and for neurologic use some years later by Symns.[7] An attempt was made to apply the fork when vibrating at a definite amplitude and to measure the time between its application and the disappearance of the sensation. A similar technic was employed by Williamson [8] and many other clinical investigators. However, Head [9] preferred the so-called alternate displacement method, which entails measurement of the elapsed time between the cessation of vibratory perception on one side and the moment when the fork, still vibrating, finally ceases to be felt after being transferred to the identical point on the opposite side.

The fatigue factor obviously interfered with any accurate estimation of the vibratory threshold by either of the aforementioned methods, as emphasized by McKinley [10] and Gordon.[11] Grandis [12] had experimented

4. von Wittich, W.: Bemerkungen zu Preyers Abhandlung über die Grenzen des Empfindungsvermögens und Willens, Arch. f. d. ges. Physiol. **2**:329, 1869.

5. Rumpf, J.: Ueber einen Fall von Syringomyelie nebst Beiträgen zur Untersuchung der Sensibilität, Neurol. Centralbl. **8**:185, 1889.

6. Gradenigo, G.: A New Optic Method of Acoumetrie, J. Laryng., Rhin. & Otol. **14**:583, 1899.

7. Symns, J. L. M.: A Method of Estimating the Vibratory Sensation, with Some Notes on Its Application in Diseases of the Peripheral and Central Nervous System, Lancet **1**:217, 1918.

8. Williamson, R. T.: Vibrating Sensation in Diseases of the Central Nervous System, Am. J. M. Sc. **164**:715, 1922.

9. Head, H.: Studies in Neurology, London, Oxford University Press, 1920.

10. McKinley, J. C.: Simple Method for Determination of Threshold Value of Vibration Sense, Proc. Soc. Exper. Biol. & Med. **25**:827, 1928.

11. Gordon, I.: The Sensation of Vibration, with Special Reference to Its Clinical Significance, J. Neurol. & Psychopath. **17**:107, 1936.

12. Grandis, V.: Sur la mesure de l'acuité auditive au moyen de valeurs physiques comparables entre elles, Arch. ital. de biol. **37**:359, 1902.

with an electrically controlled rheochord in 1902, and Minor,[13] two years later, explored "bone sensitivity" with an electromagnetically driven fork. In his meticulous experiments von Frey[14] also employed an electromagnetic fork to which was attached a bristle that would deliver vibratory stimuli in a punctate manner. The introduction of the vacuum tube oscillator into laboratory research in the last decade has brought great refinement to the experimental work on vibration. Particularly noteworthy in this field are the contributions of Geldard and Gilmer,[15] who reduced the radiation by using very small, nonrigid vibrating contacts.

The need for a clinical instrument which would be capable of measuring the vibratory threshold by increasing the amplitude of vibration has been felt for some time. A step in this direction was the pallesthesiometer built by Henney for Tilney[16] (1929), who used it in his extensive sensory examination of Helen Keller. However, this instrument in its original form provided for study of variations in frequency rather than changes in amplitude. This type of approach is of more value in the study of tactual pitch perception by the deaf than in the solution of problems of vibration sense. In 1932 Gray[17] reported on the clinical trial of an electrically operated tuning fork in which the amplitude could be controlled, but this apparatus has apparently not been employed further.

THE PALLESTHESIOMETER[18]

The instrument employed in this work is similar to that used by Tilney, except that it provides for variation in the amplitude rather than in the frequency. An electromagnetically controlled rod vibrates vertically. The frequency remains constant at 60 double vibrations per second, since the apparatus operates on a 110 volt, 60 cycle alternating

13. Minor, L.: Ueber die Localisation und klinische Bedeutung der sog. "Knochensensibilität" oder das "Vibrationsgefühls," Neurol. Centralbl. **23**:146, 199, 1904.

14. von Frey, M.: Physiologische Versuche über das Vibrationsgefühl, Ztschr. f. Biol. **65**:417, 1915.

15. Geldard, F. A., and Gilmer, B. von H.: A Method for Investigating the Sensitivity of the Skin to Mechanical Vibration, J. Gen. Psychol. **11**:301, 1934. Geldard, F. A.: The Perception of Mechanical Vibration, ibid. **22**:243, 271, 281 and 291, 1940.

16. Tilney, F.: A Comparative Sensory Analysis of Helen Keller and Laura Bridgman: Mechanisms Underlying Sensorium, Arch. Neurol. & Psychiat. **21**: 1227 (June) 1929; Its Bearing on Further Development of Human Brain, ibid. **21**:1237 (June) 1929.

17. Gray, R. C.: Quantitative Study of Vibration Sense in Normal and Pernicious Anemia Cases, Minnesota Med. **15**:674, 1932.

18. Made by the Winchester Company, 155 East Forty-Second Street, New York.

current circuit. On the end of the vibrating rod is a hard rubber button 7 mm. in diameter, which can be brought into contact with any point on the surface of the subject's body. The applicator can easily be held in the examiner's hand and is allowed to rest against the skin with its own weight (100 Gm.). A switch introduced into the circuit at the side allows the vibration to be stopped without the subject's knowledge, thus providing for frequent check on his responses. The amplitude of vibration is controlled by a potentiometer. Threshold values are measured in units from 0 to 100 on the potentiometer dial. These can be converted into units of 0.001 inch (0.025 mm.) amplitude of vibration by reference to a calibration curve furnished with each instrument. For practical purposes the thresholds recorded in this paper are uniformly recorded in dial settings, a method which is entirely satisfactory for purposes of analysis and comparison. The average C-128 fork used clinically delivers a vibratory stimulus of diminishing amplitude which corresponds to the excitatory properties of the pallesthesiometer within a range of 50 to 25 on the potentiometer dial.

FORMER EXPERIMENTAL STUDIES

Cohen and Lindley,[19] formerly working in our laboratory, have thoroughly tested this instrument under varying controlled experimental conditions and have proved both its reliability and its usefulness. In order to measure the actually delivered amplitude of vibration an auxiliary equipment was used. This consisted of an optical lever system incorporating a small concave mirror placed on the vertically oscillating rod in such a way as to reflect a beam of light onto moving photographic film. By this means they showed that increased pressure lowered the threshold of vibratory sensitivity despite actual diminution of amplitude of delivered stimulation. This is probably due to mechanical factors of increased compression of tissue, which, under such circumstances, becomes a better medium for the conduction of vibration.

In unpublished work, Cohen and Lindley studied the extent of radiation of vibration in twenty-two different areas of the body while listening with a stethoscope. The instrument was kept at a constant pressure of 50 Gm.; the dial was set at 14, which represents 0.001 inch amplitude of vibration. The radiation areas on the arms and legs are extensive and, in general, follow the longitudinal axes of the long bones. In the fleshy areas over the ventral and dorsal surfaces of the midthigh the areas are practically circular. In general, the radiation seems to follow the osteologic structure of the body.

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19. Cohen, L. H., and Lindley, S. B.: Studies in Vibratory Sensibility, Am. J. Psychol. **51**:44, 1938.

TECHNIC OF EXAMINATION

The tests were carried out in a quiet room with frequent rest periods to avoid fatigue. Complete relaxation was found to be essential, and the recumbent posture was the one of choice. The dial was first set at 0 and then slowly turned up. The subject was instructed to say "now" the instant that vibration was felt. This constituted the first reading. After a brief increase in the amplitude of vibration the dial was then gradually turned back and the subject was asked to say "now" the instant that the sensation of vibration disappeared. This constituted the second reading. The procedure was repeated one or more times, depending on the approximation of the values obtained. The dial was then set midway between the two thresholds, and the same point was retested. In similar manner neighboring amplitudes just above and below this level were explored until the final value was determined. Corresponding points on the two sides of the body were frequently checked for comparison of a given threshold. Examination was repeated at a later sitting whenever there was doubt about the thresholds.

NORMAL THRESHOLDS FOR VIBRATION

Laidlaw and Hamilton,[20] using the same apparatus and a similar experimental procedure, determined the vibratory threshold on 76 points of the body in two groups of normal subjects—40 young adults and 20 persons above the age of 50. Our results in a smaller group differ in no important degree. The modal values expressed in dial readings for the points of the body commonly used in this investigation are shown in figure 1. There is no substantial difference between the right and the left side regardless of handedness.

A rather wide range of variation exists among healthy subjects. As suggested by Laidlaw and Hamilton, it is probably advisable to consider twice the modal value as the upper limit of normal, particularly in areas of obesity and over edematous regions or calloused skin. Age is an important factor in elevation of the threshold, especially over the lower limbs and sacrum. Pearson[21] found a progressive slight decrease in vibratory sensitivity decade by decade, becoming striking after the age of 50, until it was actually lost in the lower extremities in some of the aged.

On the contrary, some subjects are peculiarly hypersensitive to vibration. Relatively lower thresholds are elicited over the fleshy areas in thin people, owing to greater proximity of the vibrator to the underlying bone. Tomson,[22] as early as 1890, noted the significance of vibratory

20. Laidlaw, R. W., and Hamilton, M. A.: Thresholds of Vibratory Sensibility as Determined by the Pallesthesiometer: A Study of Sixty Normal Subjects, Bull. Neurol. Inst. New York **6**:494, 1937.

21. Pearson, G. H. J.: Effect of Age on Vibratory Sensibility, Arch. Neurol. & Psychiat. **20**:482 (Sept.) 1928.

22. Tomson, B.: The General Appreciation of Vibration as a Sense Extraordinary, Lancet **1**:1299, 1890.

perception in the blind and deaf, and recently Tilney [16] emphasized that vibration sense plays an extremely important role in the information it conveys to Miss Helen Keller. For example, she is able to interpret spoken language by placing her hand on the face of the speaker so that the thumb rests on the larynx, the middle finger on the lips and the index finger on the ala of the nose. We found a 25 year old harpist to have uniformly low thresholds over the lower as well as the upper limbs, which may represent a specialized sensory endowment of this person as a result of her profession.

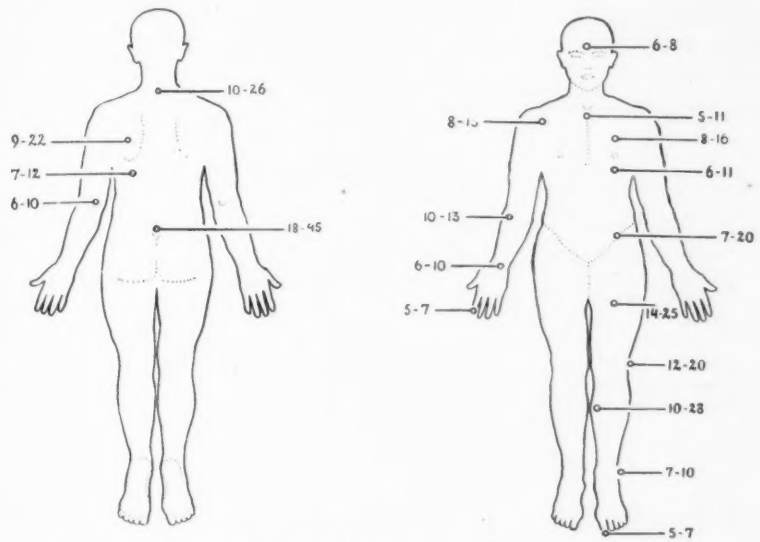

Fig. 1.—Normal thresholds of vibratory sensitivity. Modal values, expressed in dial readings, are shown for the points commonly stimulated. The left of each pair of figures refers to young adults; the right, to persons over 50.

CLINICAL MATERIAL

Determinations of the vibratory threshold were made in 66 cases of known disorders of the nervous system over a three year period, thus permitting repeated testing in many instances. Appraisal of both primary and discriminatory sensory functions was uniformly painstaking, and the results were reevaluated at each subsequent testing with the vibrator. The site and nature of the lesion were indicated by operation in 22 cases, but, unfortunately, in no case were data obtained at autopsy which were of significant value in correlation of clinical and pathologic findings. The cases are classified and arranged in the order of presentation in table 1.

Single Nerve Lesions.—Three cases, 2 of an ulnar and 1 of a median nerve lesion, all with partial loss of vibration sense, were included in this group. Thresholds of vibratory sensitivity were obtained at various points on the fingers and hand, both within and outside the hypesthetic zone. In each involved area vibratory sensitivity was decreased, but to a relatively slight extent. The highest threshold was obtained over the pad of the little finger in 1 of the cases of lesion of the ulnar nerve, as compared with a normal reading for the corresponding finger of the other hand. No difference in the thresholds was found on comparing the lateral and medial surfaces of the fourth digits in cases of involvement of either the median or the ulnar nerve. There was also no appreciable change in the threshold as the vibrator was moved across the boundary of the hypesthetic area on the hand, an observation obviously to be explained by radiation of the stimulus.

TABLE 1.—*Classification of Clinical Material*

Disorder of Nervous System	No. of Cases
Single nerve lesions	3
Multiple peripheral neuritis	9
Subacute combined degeneration	14
Focal lesions of the cord	9
Other spinal degenerative processes	8
Involvement of the brain stem	2
Cerebral lesions	17
Conversion hysteria	4
Total	66

Multiple Peripheral Neuritis.—The group of 9 cases of this condition represented various etiologic factors. In 6 cases the disturbance had a deficiency basis, in 3 of which it was associated with alcoholism and in 3 with an inadequate diet; in 1 of the latter pellagra was present as well. There was 1 case each of polyradiculitis (Guillain-Barré disease), dermatomyositis and senile neuropathy of uncertain origin. In the majority of these cases the patient was under observation in the hospital for extended periods. In 2 cases the period of study covered three years and in 1 case two years.

The profile of vibratory impairment for the entire group of 9 cases is shown graphically in figure 2. The relatively greater loss of vibratory sensitivity in the lower limbs than in the upper is evident. The pelvis and, to a less extent, the seventh cervical spine and the sternum have not escaped. The maximal impairment in the most distal portions of the lower limbs (great toes) is striking. On the contrary, this pattern

is not evidenced in the upper limbs, in which the vibratory threshold appears to be uniformly, but not greatly, elevated and the general configuration of vibratory sensibility tends to conform to the normal profile. In 7 of the 9 cases the patients had undergone no previous treatment and were in a relatively early stage of the disorder when the first readings were made. In all but 1 case the loss of vibratory sense was symmetric. Later determinations in 4 of 6 cases during the course of recovery, with thiamine treatment, gave different thresholds over corresponding points on the two sides of the body. This indicates that the rate of recovery is not always uniform.

Subacute Combined Degeneration.—Determinations were made in 9 of the 14 cases before liver therapy was started, whereas in 5 cases

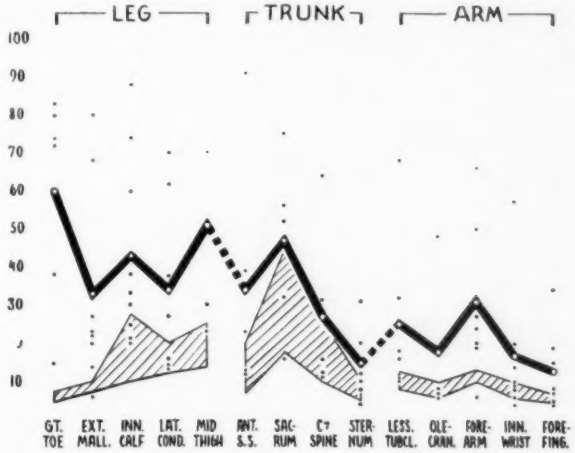

Fig. 2.—Profile of vibratory sensibility in peripheral neuritis. Points stimulated are indicated along the abscissa; thresholds of vibratory sensibility are given on the ordinate. Dots represent the average threshold values for each case. The heavy line indicates the mean for all cases of peripheral neuritis. Diagonally shaded areas denote the spread of normal modal values (indicated in figure 1).

previous treatment had been given. The profile of impairment of vibratory sense for the entire group of 14 cases is shown graphically in figure 3. The much greater loss in the lower limbs as compared with the upper and the high thresholds over the anterior superior spines and the sacrum as compared with the seventh cervical spine and the sternum should be noted. The involvement of the upper limbs is somewhat less striking than in the group of cases of peripheral neuritis (fig. 2).

Repeated readings were taken in 10 cases during treatment. The thresholds were lowered in 4 instances, remained unchanged in an equal number and became even further elevated in 2 cases. The pallesthesi-

ometer proved a particularly valuable aid in the treatment of incipient primary anemia with subacute combined degeneration (case 1).

Distal cutaneous sensory impairment and muscle tenderness are often associated with combined system disease, indicating superimposed peripheral neuropathy. This had been suspected by clinicians for many years and was confirmed by pathologic demonstration of peripheral nerve degeneration, as well as changes in the cord, long before the days of liver therapy. In addition to disturbance of proprioceptive sensation, distal cutaneous sensory impairment, usually of low sock distribution and of less than glove extent, was presented in 7 of 14 cases. In all of these cases the patients received thiamine hydrochloride, as well as liver extract, in the later stages of treatment. Although a further sub-

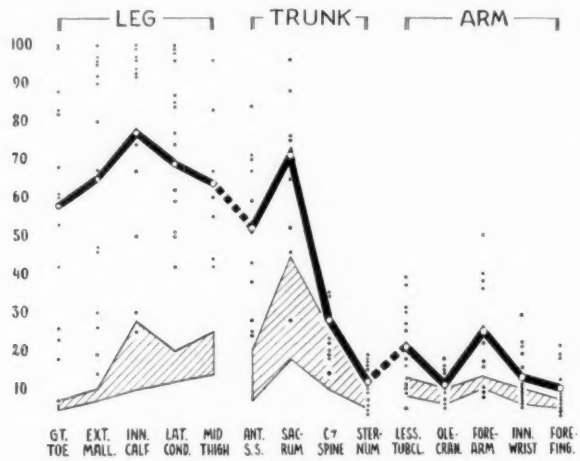

Fig. 3.—Profile of vibratory sensitivity in subacute combined degeneration. Thresholds are charted in the same manner as in figure 2. The heavy line indicates the mean for all cases of combined sclerosis.

stantial retreat in the numbness took place in all cases in which thiamine was given, in only 2 was there additional lowering of the vibratory threshold, of which case 2 is illustrative.

Focal Lesions of the Cord.—The data on this group, comprising 9 cases, 3 of cervical and 6 of thoracic lesions, are tabulated in the upper section of table 2. The fairly close correlation between the degree of loss of vibratory sensation and the impairment of position sense is apparent, regardless of the type and level of the lesion. The same relation holds true for the correlation of touch and vibration senses in this group.

TABLE 2.—*Sensory Correlation Associated with Focal and Diffuse Lesions of the Cord*

Case	Type of Lesion *	Sensory Disorder—Lower Limbs: Touch: Distal	Touch: Proximal	Position: Great Toe	Position: Ankle	Position: Knee	Loss of Vibratory Sense: Great Toe	Loss of Vibratory Sense: External Malleolus	Loss of Vibratory Sense: Calf	Loss of Vibratory Sense: External Condyle
3	Chordotomy, D 4	—	—	—	—	—	±	—	—	—
	Ruptured disk, C 7	—	—	—	—	..	±	—	—	..
	Fracture-dislocation, C 2	—	—	—	—	—	—	—	—	—
	Tumor (postoperative), D 8	—	—	—	—	—	±	..	—	—
	Arachnoiditis, D 6	++	++	++	++	++	+	++	+++	+++
11	Tumor, D 6	++	++	+++	+++	++	+++	++	+++	+++
	Arachnoiditis, cervical	+	+	+++	+++	+++	+++	+++	++	+++
	Fracture-dislocation, C 5	++++	++++	++++	++++	++++	++++	++++	++++	++++
4	Fracture-dislocation, D 7	++++	++++	++++	++++	++++	++++	++++	++++	++++
10	Myeloradiculitis	† —	—	++++	+++	+++	† +++	+++	+++	—
	Myelitis, residual	—	—	++	+	—	++	++	+	—
	Myelitis, acute	++++	++++	++++	++++	++++	++++	++++	++++	++++
	Tabes	—	—	±	±	+	++	+++	+++	+++
	Tabes	—	—	—	—	—	+++	+++	+++	+++
	Multiple sclerosis	+++	+	+++	+++	+++	+++	++	++	++
	Multiple sclerosis	—	—	+++	+++	++	+++	+++	+++	+++
	Spinocerebellar degeneration	—	—	—	—	—	+	—	±	±

* C indicates a cervical, and D, a dorsal segment.

† Refers to the upper limbs.

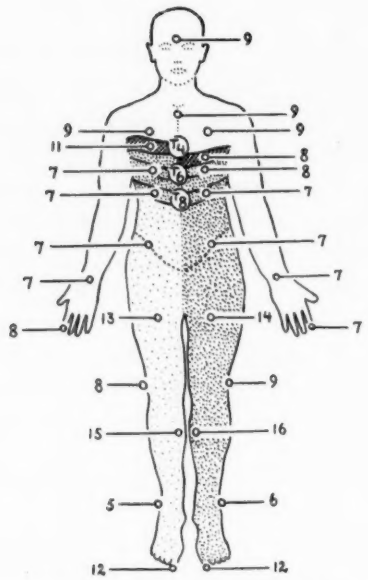

Fig. 4 (case 3).—Sensory impairment and thresholds of vibratory sensitivity following chordotomy at the fourth thoracic segment.

Zones of hyperalgesia are indicated by diagonal lines; zones of analgesia, by thickly dotted areas, and the zone of hypalgesia, by a sparsely dotted area.

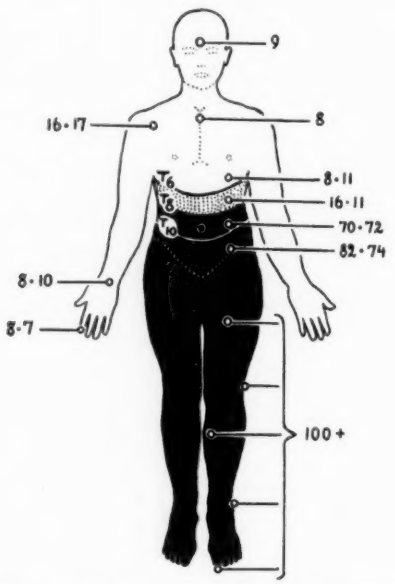

Fig. 5 (case 4).—Sensory loss and thresholds of vibratory sensibility following fracture-dislocation of the seventh thoracic vertebra with transection of the cord. In each pair of figures the numbers refer to corresponding sides of the body. The dotted area indicates the zone of hypesthesia; the black area, the zone of anesthesia.

The negative effect of section of the spinothalamic tract on vibratory sensation is demonstrated in case 3 (fig. 4). The important role of radiation of the vibratory stimulus below the level of anesthesia in cases of complete transection of the cord is shown in case 4 (fig. 5).

Other Spinal Degenerative Processes.—Eight cases made up this group, as shown in the lower section of table 2. Vibratory sensitivity was impaired in all instances in varying, but on the whole pronounced, degree. Correlation between loss of position and loss of vibratory sense held fairly well throughout, but this did not apply particularly to touch and vibration sense. In both cases of tabes the lower limbs were affected, but in neither instance was sensibility of the pelvis, as measured on the anterior superior spine and the sacrum, significantly diminished

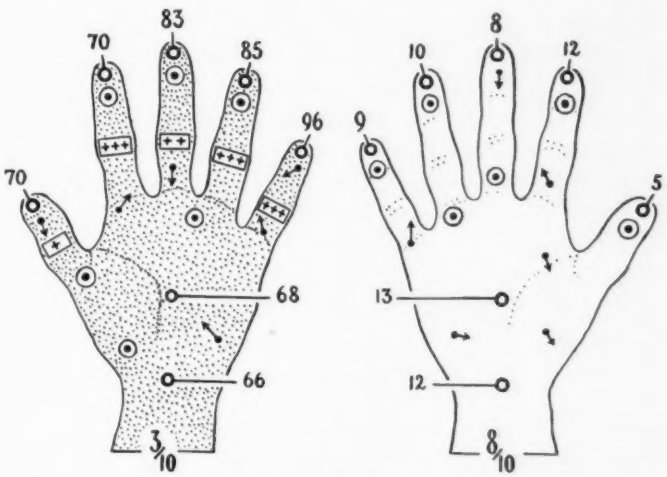

Fig. 6 (case 5).—Sensory disturbance and thresholds of vibratory sensibility in a case of compression of the brain stem due to platybasia. The degree of loss of position sense in the phalangeal joints is indicated by +, ++ and +++; accurate topognosis is designated by a circle and dot, and the amount of displacement, by the arrow. Areas of hypesthesia are indicated by dots. The measure of stereognosis is represented by a fraction; the numerator equals the number of articles identified, and the denominator, the total number tested for.

when allowance was made for the patient's age. This finding must be considered atypical because the loss of vibratory sense over the sacrum in tabes has been emphasized clinically for many years.[8] It is of interest that both patients were impotent and the threshold for the glans penis was elevated in each instance—64 and 68, respectively. The range of normal values for this organ is from 15 to 30.

Lesions of the Brain Stem.—In the first case the neurologic picture of thrombosis of the left posterior inferior cerebellar artery was presented. Vibratory sensation was everywhere within or just above

TABLE 3.—*Classification of Cerebral Lesions According to Impairment of Vibratory Sensibility*

Case	Location	Type of Lesion	Operative Procedure	Interval After Operation	Sensory Disorder					Vibratory Loss			
					Touch	Pain	Position	Local	Stereognostic	Hand	Arm	Foot	Leg
	R. frontal	Cerebral atrophy	Exploration	.....	—	—	—	—	—	—	—	—	—
	L. frontal	Meningioma	Removal	15 mo.	—	—	—	—	—	—	—	—	—
	L. frontal	Scar	Excision of scar	15 mo.	—	—	—	—	—	—	—	—	—
	Bifrontal	Meningioma	Removal	15 mo.	—	—	—	—	—	—	—	—	—
	L. frontal	Thrombosis (?)	.....	.....	..	—	—	—	±	—	—	—	—
	L. frontoparietal	Meningioma	.....	Preoperative	—	—	+	+++	..	—	—	—	..
6	L. parietal	Cortical thrombosis (?)	.....	.....	+	—	++	±	++	—	..	..	..
	R. parietal	Meningeal cortical scar	Excision of scar 3 cm. deep	1 yr.	—	—	++	++	+	—	—	—	—
	R. occipital	Lobectomy (1st stage pinealectomy)	Transection 3.5 cm. anterior to pole	4 yr.	—	—	—	—	—	—	—	—	—
	R. occipital	Lobectomy (scar)	Transection 3.5 cm. anterior to pole	3 yr.	—	—	—	—	—	—	—	—	—
	R. frontoparietal	Thrombosis	.....	.....	—	—	±	..	+	+	—	+	..
	L. cerebral	Porencephaly	Exploration	.....	+	+	+	+	—	—	+	—	+
	R. parietofrontal	Fibromyxosarcoma	Partial removal	(1) Preoperative	..	..	+	—	—	+	+	+	..
				(2) 3 yr.	..	..	+++	+	±	—	±	+	+
9	L. parietal	Porencephaly	Resection to ventricle	(1) 2 mo.	+	+	+++	+++	+++	++	++	+++	+++
				(2) 3 yr.	—	—	+++	+++	+++	—	—	—	+
	L. parietotemporal	Glioma	.....	Preoperative	+	+	++	+++	+++	++	++	+	+
	L. temporoparietal	Abscess	Drainage	1 yr.	—	—	+++	..	+++	+++	++	+	++
7	L. frontoparietal	Astrocytoma	Partial removal	5 mo.	+	+	+++	+++	+++	+++	+++	+	+

the range of normal, but there was no difference between the thresholds on the two sides of the body. Case 5 was one of platybasia with compression of the medulla, which provided an ideal opportunity for study of loss of vibratory sense from a lesion at this level (fig. 6).

Cerebral Lesions.—The 17 cases of disease of the brain are listed in table 3. The location and nature of the lesion were determined as far as possible by exploration in 13 instances and further differentiated by biopsy in all but 1 of these. The upper section of table 3 contains the data on 10 cases in which vibratory sense was not disturbed; the lower section, the data on 7 cases of impairment of vibratory sense. In the first, or negative, group are 7 control cases—5 of frontal and 2 of occipital lesions without sensory involvement, in which no vibratory impairment would be expected. However, the vibratory threshold likewise was not raised in the 3 cases of a parietal lesion, which otherwise affected kinesthetic, topognostic and stereognostic sense. Significant is the fact that the lesion in each instance was relatively superficial, interfering only with cortical function. Illustrative of this point is case 6 (fig. 7).

In striking contrast, in all 7 of the cases listed in the lower section of table 3, in which vibration sense was affected, lesions involved the subcortical region of the brain. The degree of impairment seemed to bear a direct relation to the depth and extent of the lesion, as revealed by operative procedures in 6 cases. A severe degree of loss of vibratory sense was produced by a deeply infiltrating glioma in case 7 (fig. 7).

Certain characteristics of the disorder in vibratory perception associated with cerebral lesions stand out. There was no predilection for either the proximal or the distal portion of the affected limb. The little and ring fingers frequently showed a higher threshold than the other digits, an observation which is in line with Head's claim that the "ulnar" side of the hand is often the more vulnerable in sensory disturbances of cerebral origin.[9] Various dysesthesias of vibration were encountered, such as delayed perception, uncertainty of response, widened span between thresholds for increasing and decreasing amplitudes and susceptibility to fatigue. Occasionally, even when the threshold was normal, the patient might describe the sensation as "different" from, or even "stronger" than, that elicited by the same stimulus at a corresponding point on the opposite side.

Conversion Hysteria.—Four cases of conversion hysteria were studied with the pallesthesiometer. The findings in each instance refuted the principle of radiation of the stimulus through neighboring skin and deeper tissues. In a case of right hemihypesthesia for all forms of sensation the vibratory threshold was elevated right up to the midlne, but the levels varied considerably over different points on the involved side.

In a second case, in which a circumferential band of hypesthesia was present at the elbow, variously elevated thresholds for vibration were noted within the boundaries of the hypesthetic zone. In a third case, in which there was complete anesthesia below the elbow, no vibration

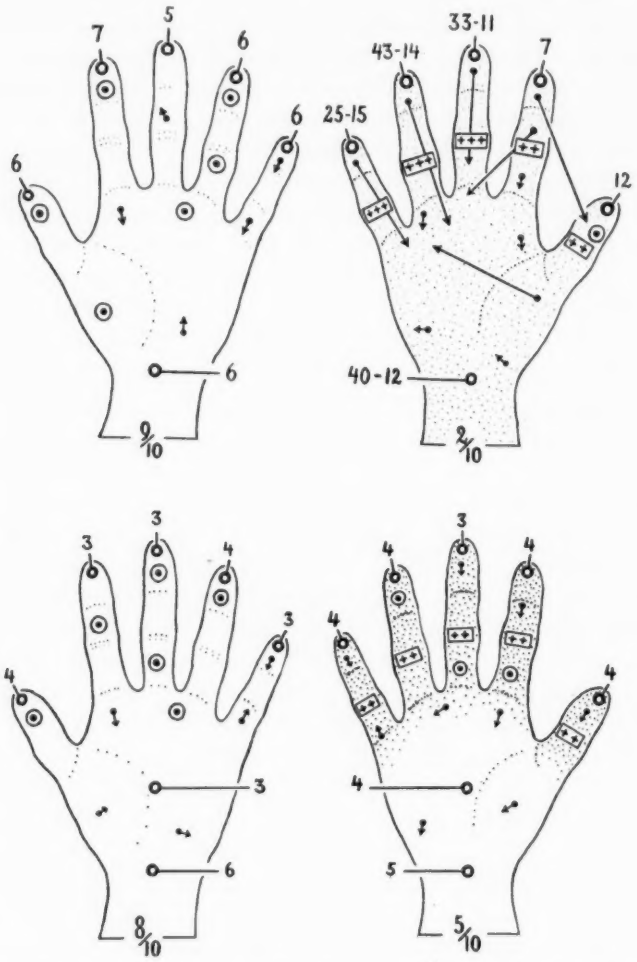

Fig. 7.—Comparison of sensory disturbance and thresholds of vibratory sensitivity in 2 cases of cerebral lesions on the left side. The lower pair of hands are those of a patient with impairment of cortical function of vascular origin (case 6) ; the upper pair, those of a patient with a deeply infiltrating glioma (case 7). Symbols are the same as those in figure 6. Areas of hypesthesia are indicated by dots.

distal to the line of demarcation was reported. Recovery of vibratory sensibility ran parallel to the return of the other modalities, as demonstrated in case 8 (fig. 8).

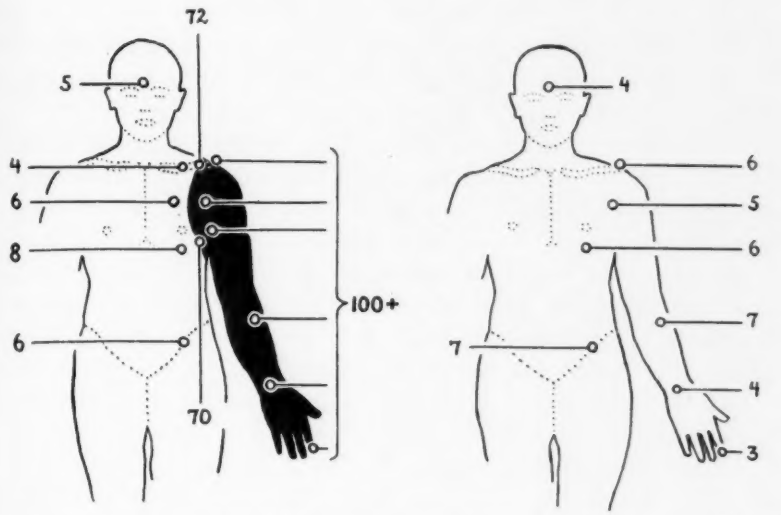

Fig. 8.—Zone of anesthesia and thresholds of vibratory sense in a case of conversion hysteria (case 8), at the height of the disorder and after recovery. The area of anesthesia is indicated by solid black.

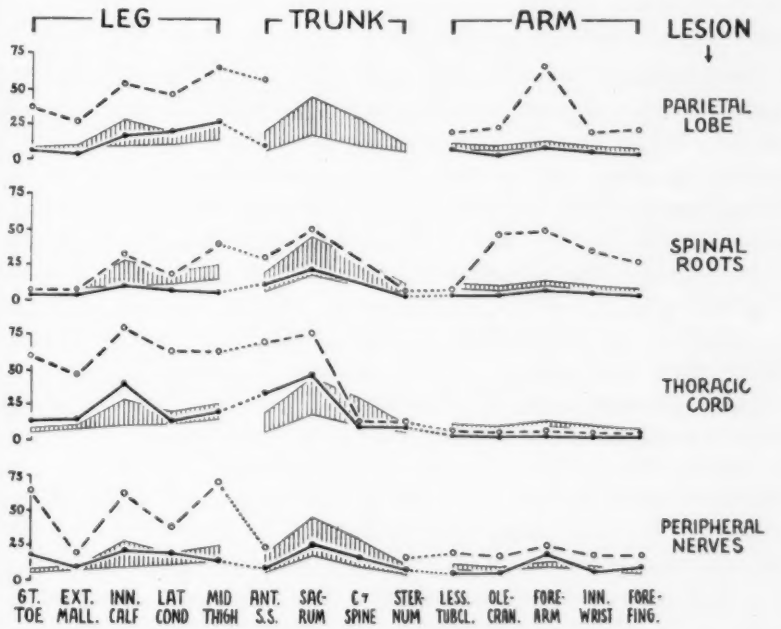

Fig. 9.—Profiles showing patterns of recovery of vibratory sense in 4 cases of variously situated lesions. Thresholds are charted in the same manner as in figures 2 and 3 except for the shortening of the ordinates. The broken line refers to first readings; the unbroken line, to final readings. Profiles in order from above downward are those for cases 9, 10, 11 and 12.

RECOVERY OF PALLESTHESIA

The nervous system possesses the capacity for complete restoration of vibratory sensibility regardless of the site of the lesion, provided of course the damage has not been irreparable. Recovery may take place even after severe loss has occurred. This was well demonstrated after varying intervals in 4 cases for which the profiles for impairment of vibratory sense are charted in figure 9. The profile at the top (case 9) shows the capacity for restitution of function even after extensive damage to the subcortical region as well as to the sensory cortex. The next (case 10) illustrates rapid recovery of vibratory sensibility, ahead of kinesthesia, after acute myeloradiculitis involving chiefly the cervical region. The third (case 11) displays an amazingly rapid improvement in vibratory sense within eleven days after surgical relief of compression of the spinal cord. The possibility of final restoration of pallesthesia three years after severe peripheral neuritis is evidenced in case 12.

COMMENT

The major aim of this work has been to provide the clinical neurologist with further data on impairment of the vibratory sense in disease of the nervous system. However, certain deductions regarding the reception, transmission and perception of vibration seem warranted.

Receptors.—The cases with involvement of the peripheral nerves were studied with particular reference to correlation between elevation of the vibratory threshold and impairment of cutaneous and proprioceptive sensation. In 1 of the cases of a single nerve lesion (ulnar), in spite of anesthesia of the skin for touch, vibratory sense was only slightly impaired. It is obvious that vibration is not dependent on stimulation of touch endings alone, a fact which has been demonstrated many times by anesthetization experiments, such as the recent ones of Cohen and Lindley,[19] in which intradermal injection of procaine caused no change in the vibratory threshold.

In all the cases of peripheral nerve lesions, whether single or multiple, the vibratory threshold varied considerably, depending on the degree of pressure exerted on the point stimulated, especially over fleshy areas, and tended to approach normal as the skin was depressed by the vibrating button. This is explained by two factors—radiation of the vibratory stimulus and excitation of the deep receptors. Strange indeed is the fact that conduction of vibration has been so largely disregarded in many of the speculative theories concerning the mode of its reception! That the proprioceptive receptors do not play the sole role is indicated by the occasional preservation of position sense in spite of severe impairment of vibratory sense. This type of "dissociation" was found in one

third of the 9 cases of peripheral neuritis. It appeared that pallesthesia suffered most when both tactile and kinesthetic sense were severely impaired, whereas in no instance was vibratory sense affected when both of these modalities had escaped. No correlation whatever could be demonstrated between change in the vibratory threshold and alteration of pain and temperature sensitivity, whether increased or decreased.

All of these findings seem to speak for dual receptors for the vibratory stimulus by both cutaneous and proprioceptive endings. Pollock,[23] in his demonstration of preservation of vibratory sense following section of the sensory root of the fifth cranial nerve, adduced further evidence that the apperception of repetitive stimuli must pertain to both cutaneous and deep receptors. But even more crucial proof is offered by the experimental studies of Echlin and Fessard [24] and Newman, Doupe and Wilkins.[25] The former recorded from the nerve of a cat action potentials which were synchronous with the vibrations of a tuning fork applied to its related muscles or their tendons. The latter reported that they obtained potentials from a nerve to an isolated piece of skin which also had the same frequency as the vibrating fork. Recently Pfaffmann [26] has shown that application of a vibrating stylus to the surface of an intact tooth gives rise to an oscillatory discharge to the dental nerve which is synchronized with the stimulus frequency.

Pathways.—With respect to the spinal transmission of vibratory impulses many questions remain unanswered. The spinothalamic tract obviously plays no signficant role, as shown by preservation of pallesthesia after chordotomy (case 3). Lesions of the posterior columns usually affect vibratory sense, as judged by the fairly close correlation between loss of position sense and impairment of vibratory sensibility. In our total series of 33 cases of lesions of the spinal cord and brain stem there was no instance in which vibratory sensitivity escaped and position sense was impaired. However, the opposite situation held true in 8 cases.

Dissociation between kinesthesia and pallesthesia has plagued the physiologist, as well as the clinician, for many years. Pathologic studies by Hamilton and Nixon [27] twenty years ago in 10 cases of subacute com-

23. Pollock, L. J.: Vibration Sense, Arch. Neurol. & Psychiat. **37**:1383 (June) 1937.

24. Echlin, F. A., and Fessard, A.: La sensibilité vibratoire et le percepteur de tension, Compt. rend. Soc. de biol. **124**:1199, 1937.

25. Newman, H. W.; Doupe, J., and Wilkins, R. W.: Some Observations on the Nature of Vibratory Sensibility, Brain **62**:31, 1939.

26. Pfaffmann, C.: Afferent Impulses from Teeth Resulting from Vibratory Stimulus, J. Physiol. **97**:220, 1939.

27. Hamilton, A. S., and Nixon, C. E.: Sensory Changes in the Subacute Combined Degeneration of Pernicious Anemia, Arch. Neurol. & Psychiat. **6**:1 (July) 1921.

bined degeneration revealed the disharmony between the degenerative changes in the posterior columns and the loss of vibratory sense. Laidlaw, Hamilton and Brickner [28] reported in detail 20 cases of dissociated disturbances of vibratory and postural sense associated with spinal disease, about equally divided between the two types of impairment. More recently Weinstein and Bender [29] claimed that in cases of dissociation of deep sensibility vibratory sense tends to fare the worst when the lesion is at the thoracic or lumbar level, whereas postural sense is more likely to be affected when the lesion is in the brain stem. Various explanations have been offered for this "dissociation" since the turn of the century. These postulate either separate pathways in the posterior column for each modality or a second pathway for one or the other sense, located in the dorsal spinocerebellar tract or elsewhere in the cord.

Histopathologic studies were not available in any of our 8 cases in which vibratory sense was impaired and position sense unaffected, chiefly because clinical improvement took place with liver therapy in the 6 cases of subacute combined degeneration. But it may be significant that in 4 of these cases there was some degree of tactile impairment as well, which may explain the diminution of vibratory sense. In fact, search for the "vibratory pathway" in the cord has failed to take into account transmission via the conduction system for contact and pressure sensations. Whether these fibers are bilaterally represented and are situated in other tracts as well as in the posterior column is still under debate. But if the vibratory stimulus is capable of exciting both cutaneous and deep receptors it may be transmitted along multiple spinal pathways as well. This is particularly true if pallesthesia is not a specific sense but a composite functional expression of various modalities, as will be discussed later. In fact, its impairment in cases of disease of the spinal cord may well depend on the aggregate number of subserving pathways interrupted rather than on the severing of any particular tract.

Perception.—Head [9] made the following statement: "above the point where the fillet ends in the optic thalamus no lesion produces complete insensibility to vibration except under conditions of neural shock." This conclusion, based on a far less refined technic than that used in his studies of other sensory functions, has remained essentially unchallenged during the past two decades. Holmes [30] remarked that the tuning fork test is

28. Laidlaw, R. W.; Hamilton, M. A., and Brickner, R. M.: The Occurrence of Dissociated Disturbances of Pallesthesia and Kinesthesia, Bull. Neurol. Inst. New York **7**:303, 1938.

29. Weinstein, E. A., and Bender, M. B.: Dissociation of Deep Sensibility at Different Levels of Central Nervous System, Arch. Neurol. & Psychiat. **43**:488 (March) 1940.

30. Holmes, G.: Disorders of Sensation Produced by Cortical Lesions, Brain **50**:413, 1927.

one of the least useful in cases of cortical disease because there is usually, at the most, only a subjective difference between the involved part and its normal fellow. In a study of the sensory defects resulting from cerebral ablations, Evans,[31] employing a C-256 fork, found relatively slight and circumscribed impairment of vibratory sensibility. The exception was a case of excision of a large block of tissue in the region of the right supramarginal gyrus, in which there was a gross loss of vibration sense at the elbow, wrist, knee and ankle on the left side (cf. case 9).

Marie and Bouttier [32] in 1922 had expressed doubt as to the parallelism between the loss of postural and that of vibratory sense in cases of cerebral lesions, a doubt which was later shared by Holmes.[30] Laidlaw, Hamilton and Brickner,[28] using a quantitative technic for both kinesthesia and pallesthesia, demonstrated true dissociation in 4 instances. Weinstein and Bender [29] found that appreciation of vibration was spared or slightly affected in 7 patients with cerebral lesions who at the same time suffered pronounced disturbance of position sense, stereognosis and two point discrimination.

Our results with the pallesthesiometer indicate that the perceptive *threshold* for vibration is not affected by a cortical lesion. This refers not only to disturbance of the blood supply of the sensory cortex but to compression of the parietal region and may even apply to excision of tissue in the supramarginal gyrus to a depth of 3 cm. It would appear that the sensory cortex plays merely a modifying role, as indicated by the subjective alteration of vibration sensibility noted even with superficial lesions.

However, involvement of the subcortical structures usually causes some elevation of the threshold. A deeply infiltrating glioma, a widely extending abscess or resection of brain tissue to the ventricle in the posterior parietal lobe constituted sufficient damage to raise notably the vibratory threshold. The restitution of vibratory sensibility after three years in case 9, although other cortical sensory functions remained severely impaired, is further evidence that integrity of the cortex is not essential to perception of vibration. Vibration sensation may resemble weight lifting in this respect. Ruch, Fulton and German [33] found that in both man and chimpanzee relatively large areas of the parietal cortex may be damaged without greatly disturbing the discrimination of lifted

31. Evans, J. P.: A Study of the Sensory Defects Resulting from Excision of Cerebral Substance in Humans, A. Research Nerv. & Ment. Dis., Proc. **15**:331, 1934.

32. Marie, P., and Bouttier, H.: Etudes cliniques sur les modalités des dissociations de la sensibilité dans les lésions encéphaliques, Rev. neurol. **29**:1, 1922.

33. Ruch, T. C.; Fulton, J. F., and German, W. J.: Sensory Discrimination in Monkey, Chimpanzee and Man After Lesions of the Parietal Lobe, Arch. Neurol. & Psychiat. **39**:919 (May) 1938.

weights. It is likely that functions of a temporal pattern can be subserved by nontopographically arranged systems and hence are not focally represented.

NATURE OF VIBRATORY SENSATION

In retrospect, it is amazing that Egger's [34] suggestion in 1898 that the tuning fork test was essentially one of "bone sensibility" should have elicited a clinical following for so many years. The simple expedient of testing for vibration sense on the abdominal wall distant from osseous structures or on the breast or penis should have dispelled such a notion. Also, the painstaking contributions of von Frey [14] established beyond doubt the important relation of vibration sensitivity to the pressure sense. This is not the place to discuss the typical German controversy which later ensued between von Frey and Katz,[35] who argued that the vibratory sense was a specific and separate modality. There is no doubt that the belief that vibration sensation is a sense quality *sui generis* has led to much confusion in clinical neurology. Instead, it should be thought of as a functional form or elaboration of the touch, pressure and position senses. The ability to perceive vibration is the capacity to appreciate repetitive tactile stimuli or successive pressure variations through summation. Pallesthesia is analogous to two point discrimination in so far as each is an elaboration of the primary contact sense—the former representing a concept of temporal sequence, the latter one of spatial variation. It is probably no more correct to speak of vibratory sense in tactual perception than of a flicker sense in visual perception or of a flutter sense in auditory perception.

SUMMARY AND CONCLUSIONS

The pallesthesiometer used in this work provides for variation in the amplitude of vibration of an electromagnetically controlled rod which oscillates vertically at a constant frequency of 60 double vibrations per second.

Threshold values obtained with this instrument under varying controlled experimental conditions have proved its reliability and usefulness.

Modal values, as determined for a group of normal subjects, were found to increase with age and corresponded closely with the determinations of other observers for similar points of the body.

Sixty-six cases of known disorders of the nervous system were studied over a period of three years, thus permitting repeated testing in many cases.

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34. Egger, M. M.: La perception de l'irritant sonore par les nerfs de la sensibilité générale, Compt. rend. Soc. de biol. **50**:815 and 817, 1898.

35. Katz, D.: The Vibratory Sense and Other Lectures, University of Maine Studies, series 2, no. 14, Orono, University of Maine, 1930, p. 90.

For purposes of comparison profiles were charted, showing impairment of vibratory sensibility in 9 cases of peripheral neuritis and in 14 cases of subacute combined degeneration.

The negative effect of section of the spinothalamic tract on vibratory sensation and the important role of radiation of the vibratory stimulus below the level of anesthesia in cases of complete transection of the cord are demonstrated.

The pallesthesiometer served as a useful device in the analysis of the anesthetic zone in cases of conversion hysteria and of the recovery pattern in cases of variously located lesions.

The evidence gained from correlation of pallesthesia with touch sense and kinesthesia in cases of peripheral lesions strongly favors the idea of dual receptors, both cutaneous and proprioceptive, for the vibratory stimulus.

Lesions of the posterior columns usually affect vibratory sensation, but if the vibratory stimulus is capable of exciting both cutaneous and deep receptors, it must also be transmitted by multiple spinal pathways. Vibratory impairment in disease of the spinal cord may well depend on the aggregate number of subserving pathways interrupted rather than severing of any particular tract.

Although often subjectively modified, vibration sensibility does not suffer elevation of its perceptive threshold in cases of cortical lesions, in spite of involvement of other discriminatory sensory functions.

Deeper subcortical lesions in the parietal region cause impairment of vibratory perception, but whether involvement of the optic thalamus is necessary or merely interruption of the thalamocortical connections is adequate is not answered by the available data.

Vibratory sensation should be conceived of not as a specific modality but as a functional form or elaboration of the primary senses—touch, pressure and position. In its temporal aspect for tactual perception it is analogous to flicker sense in visual perception and to flutter sense in auditory perception.

REPORT OF CASES

CASE 1.—*Subacute combined degeneration.*

A woman aged 38 with achlorhydria had a blood picture characteristic of primary anemia. Hypesthesia of the glove and high sock distribution and impairment of position sense in the feet were noted. Tests with the C-128 fork failed to show diminution in vibratory sensibility. The first quantitative elevation of thresholds occurred in the upper and lower limbs. Eight determinations of vibratory sensitivity during parenteral administration of liver extract and thiamine therapy revealed progressive return to normal .

CASE 2.—*Subacute combined degeneration.*

A man aged 56 showed a striking and sustained recovery of neurologic function over a seven year period while receiving adequate amounts of liver extract orally. He complained of distal paresthesia, and hypesthesia of high sock distribution

persisted. The vibratory thresholds were greatly elevated in the lower limbs and the pelvis (75 to 95). Distal dysesthesia retreated, and the vibratory thresholds fell (60 to 72) after additional oral administration of 10 mg. of thiamine hydrochloride daily for six months. Vibratory sensitivity was not affected further by ten weekly injections of 50 mg. each of the thiamine hydrochloride.

CASE 3.—*Chordotomy at the fourth thoracic level.*

A man aged 33 had minimal neurologic signs of tabes. Cutaneous sensibility was preserved. Serologic alteration was effected by antisyphilitic treatment. Paroxysms of epigastric pain persisted. Sensory examination following chordotomy (fig. 4) indicated complete section of the right spinothalamic tract and incomplete section of the left. Vibratory sensation was intact on both sides below the level of the lesion except in the great toe.

CASE 4.—*Transection of the cord below the eighth thoracic segment.*

A man aged 26 received a fracture-dislocation of the seventh thoracic vertebra. He survived for six years, with no return of motor or sensory function below the level of the lesion. Vibration was perceived over the trunk at a considerable distance below the level of the lesion (fig. 5). When the vibrator was placed 5 cm. to the left of the umbilicus, vibration was referred to the surface of the thorax inside the nipple. At the corresponding point on the right side sensation was transmitted "inward." He described the sensation thus: "If you can imagine gas running through the intestine as a buzz."

CASE 5.—*Platybasia, with medullary compression.*

A man aged 54 had neurologic involvement of the left fifth cranial nerve; bilateral absence of the gag reflex and lingual atrophy; left hemiparesis, with sparing of the face; pronounced nystagmus on left lateral gaze, and disturbance of cerebellar function in the left arm and leg. A roentgenogram showed evidence of platybasia. Operation revealed strangulation of the left cerebellar tonsil, with compression and indenting of the medulla just to the left of the calamus scriptorius. Vibratory thresholds determined fifteen months later are shown in figure 6. In addition to severe loss of vibratory sensibility in the left hand, cutaneous hypesthesia (all forms), pronounced astereognosis and loss of position sense were present.

CASE 6.—*Cerebral lesion without impairment of vibratory sense.*

A man aged 37 had sudden development of transitory numbness and weakness of the entire right side and dysphasia. Neurologic residual signs two months later were limited to clumsiness and sensory disturbance in the right hand. As shown in the right of the lower pair of hands in figure 7, hypesthesia (touch) in the fingers, impairment of position sense in the phalangeal joints and astereognosis were present. Vibratory thresholds were unaffected.

CASE 7.—*Cerebral lesion with vibratory impairment.*

In a woman aged 24 symptoms of increased intracranial pressure and focal signs of tumor of the left frontal lobe developed over a period of three months. Operation disclosed an astrocytoma beneath the surface of the cortex of the second frontal convolution on the left side, which had invaded through to the median fissure and had infiltrated the deep marginal areas at the site of its attempted removal. Progressive sensory disturbance was present on the right side. As shown in the right of the upper pair of hands in figure 7, sensory disturbance was present five months after craniotomy, consisting of slight cutaneous hypesthesia (all forms), severe astereognosis and atopognosis and loss of position sense, especially in the third, fourth and fifth digits. Vibratory thresholds were elevated for the tips of all fingers except the index.

CASE 8.—*Conversion hysteria.*

A youth aged 19 had anesthesia and motor paralysis of the left arm after a blow just below the elbow. The border of the anesthetic zone at first corresponded to the "amputation line" but later extended proximally, as shown in figure 8. No vibration was felt at maximum amplitude over any point within the anesthetic area, even when the vibrator was placed over the outer end of the clavicle. A consistent threshold of vibration sensitivity of 70 to 75 was felt at the boundary. Normal thresholds were noted just outside the anesthetic zone. Pallesthesia returned dramatically to normal, with other modalities.

CASE 9.—*Recovery of pallesthesia following removal of a lesion of the parietal lobe.*

A woman aged 32 had suffered from right-sided seizures since the age of 15. Paresis, astereognosis, atopognosis and impairment of position sense were noted on the right side. Vibratory sense was intact on this side. Exploration revealed a cortical scar with porencephaly in the region of the left supramarginal gyrus. A block of cerebral tissue, measuring 3.5 by 3.5 by 2.0 cm., was removed. The motor and sensory disorder on the right side increased; the severity of the epilepsy diminished. Two months later vibratory thresholds were elevated in the right arm and leg (first case; fig. 9). Three years later vibration sensitivity had returned to approximately normal, although position sense, localization and stereognosis were still defective (table 3).

CASE 10.—*Recovery of pallesthesia; myeloradiculitis.*

A woman aged 20 noted "ascending" numbness and muscular weakness, which localized in the arms three weeks after onset. Cutaneous sensation (all forms) was intact, but position sense was severely involved (table 2). The vibratory thresholds at this stage were at first slightly elevated in the legs and trunk and moderately elevated in the arms (second case; fig. 9). Ten weeks after onset readings for vibratory thresholds had returned to normal.

CASE 11.—*Recovery of pallesthesia; removal of tumor of the cord.*

A woman aged 33 had progressive paraplegia over a period of four months, with beginning retention of urine. An uncertain sensory level was noted at the fourth dorsal dermatome. Position sense was moderately impaired (table 2). There was partial spinal block. Vibratory sensibility was severely impaired in the lower limbs and the pelvis prior to operation (third case; fig. 9). An intradural meningioma was removed at the level of the third dorsal vertebra, where it had compressed the posterolateral aspect of the cord. Eleven days after operation position sense was restored; vibratory thresholds were approaching normal everywhere.

CASE 12.—*Recovery of pallesthesia; peripheral neuritis.*

A woman aged 28 showed far developed signs of peripheral neuritis, confined to the lower limbs, after gastrointestinal disturbance and loss of weight of seven months' duration. In addition, a diagnosis of dermatomyositis was made and confirmed by biopsy. Position sense was slightly and vibratory sensibility was severely impaired in the great toes (fourth case; fig. 9). Three years after an initial course of thiamine hydrochloride, at first given parenterally and later orally, plus vitamin B complex, there was no trace of loss of position sense. Vibration sensibility was normal except in the great toe.

789 Howard Avenue.

News and Comment

AMERICAN BOARD OF NEUROLOGICAL SURGERY

At a meeting of the American Board of Neurological Surgery held in Chicago, June 15 and 16, 1942, the following candidates successfully passed the examination, and their certificates will be issued two years from the date their training was completed: *Walter D. Abbott, Des Moines, Iowa; James G. Arnold Jr., Baltimore; *Edwin Barkley Boldrey, San Francisco; *J. Rudolph Jaeger, Denver; Howard H. Karr, Chattanooga, Tenn.; Samuel Lowis, Boston; George L. Maltby, Cincinnati; William A. Nosik, Cleveland; Axel K. Olsen, Sayre, Pa.; Irving J. Speigel, Chicago; James L. Thomson, Richmond, Va.; Milton Tinsley, Chicago, and Laurence M. Weinberger, Chicago.

At a meeting of the American Board of Neurological Surgery held in New York, May 12 and 13, 1942, the following specialists were certified: Eldrige Campbell, Albany, N. Y.; Francis A. Carmichael, Kansas City, Mo.; Francis A. Echlin, New York; Theodore C. Erickson, Madison, Wis.; William T. Grant, Los Angeles; Everett G. Grantham, Louisville, Ky.; William Tracy Haverfield, Jacksonville, Fla.; Franklin Jelsma, Louisville, Ky.; Abraham Kaplan, New York; John Martin, Chicago; Russell Meyers, Brooklyn; J. Lawrence Pool, New York; Bronson Sands Ray, New York; Henry G. Schwartz, St. Louis; Joseph H. Siris, Brooklyn, and James C. White, Boston.

* Certified in full.

APPOINTMENT OF CHIEF OF DIVISION OF NEUROPSYCHIATRY OF ARMY

Appointment of Dr. Roy D. Halloran, superintendent, Metropolitan State Hospital, Waltham, Mass., as Chief of the Division of Neuropsychiatry of the United States Army, with the rank of colonel, has been announced.

Assigned to the Surgeon General's Office, Colonel Halloran will coordinate the neuropsychiatric service in the Army both in this country and overseas. He assumed his new duties on Aug. 17, 1942.

Obituaries

PROF. MANUEL BALADO
1897–1942

On May 23, 1942 a great figure disappeared from the field of neurosurgery—Prof. Manuel Balado.

Dr. Balado was born in Buenos Aires, Argentina, on May 6, 1897 and received his doctoral degree from the Faculty of Medical Sciences of that city in 1921. A little later, he received a fellowship from the University of Buenos Aires and the Rockefeller Institute and carried out some experimental work in neurosurgery at the Mayo Clinic. On his return, he was appointed chief of clinic and assumed the direction of the section of neurosurgery in the Institute of Clinical Surgery, under the charge of Prof. José Arce. After demonstrating his brilliant ability as a teacher, he was appointed professor of neurosurgery in 1937, shortly after the creation of the chair.

His scientific productivity was widely recognized, as is shown by his position of vice president of the Second International Neurological Congress, held in London in 1935, and of the Third International Neurological Congress, held in Copenhagen just before the outbreak of the present world war. He received the Lagleyze Prize in 1927. On several occasions he reported on various subjects at scientific congresses at home and abroad. He took part in the preparation of the "Golden Book," presented to Professor Marinesco.

He began his intense scientific labors before going to the United States with papers on lymphogranulomatosis, on the spinal fluid and spinal anesthesia and on the mechanism of alteration in pupillary diameter in cases of intracranial hypertension. During his stay at the Mayo Clinic, he perfected new methods of staining, which permitted him to complete an anatomicophysiologic study of the innervation of the iris.

On returning to Buenos Aires, he devoted himself to neurosurgery, founding a school and demonstrating his ability as a teacher, particularly by his lectures.

One of his first studies concerned the localization of cerebral tumors, and he originated the method of iodoventriculography. His profound knowledge of the anatomy and histology of the nervous system led him to undertake a detailed analysis of the visual pathways and their pathology. Among the papers in this notable series were: "Contribution to the Anatomic Study of Quadrant Hemianopias"; "Mode of

Entrance of the Optic Tracts into the Geniculate Body in the Human Being"; "Alternating Degeneration of the Layers of the Geniculate Body in Man"; "Structure of the Normal External Geniculate Body"; "Histologic Structure of the Layers of the Body of the Corpus Geniculatum in Man"; "The Pregeniculate Body in the Human Being"; "The External Geniculate Body of the Maimon"; "The External Geniculate Body of the Mangabey"; "The External Geniculate Body of the Chimpanzee, the Orang-utan and Cebus," and other contributions on the same theme, which cannot be mentioned because of lack of space. The results of this series of investigations were so outstanding that Professor Balado prepared on request a section on the subject for the "Handbuch" of Bumke and Foerster.

He later described a new nosologic entity, that of chiasmal arachnoiditis, which was presented by Professor Arce at the Congress of Paris under the title of Balado's disease. A long series of studies led to a description of a new disorder, chronic cerebral edema.

On returning from a period of intensive study in Europe, he settled down to an investigation of the bioelectric activity of the brain, in its relationship to neurosurgery, and recorded his results in his article, "The Electroencephalogram of the Human Brain."

Not only did he organize the department of neurosurgery, but he founded the *Archivos Argentinos de neurología,* which carried abroad the news of the constant progress in this field in Argentina. He attracted many pupils to his specialty.

The extensive scientific learning and extraordinary surgical skill of this great worker were ornamented by profound literary, philosophic and artistic culture. The illustrations of his articles were the product of his own skill in drawing. To accompany him to an exhibit of paintings was to enjoy a rich feast of technical appreciation, which revealed the taste of a true artist.

An all too short life, consecrated to the solution of the problems of the anatomy and physiopathology of the nervous system, has come to an end. With the death of Professor Balado science has lost one of its great figures.

RICARDO MOREA, Buenos Aires, Argentina.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

DEMONSTRATION OF THE BASILAR ARTERY AND ITS BRANCHES WITH THOROTRAST. A. B. KING, Bull. Johns Hopkins Hosp. **70**:81 (Jan.) 1942.

King injected thorium dioxide into the vertebral artery of a Negro aged 40. The artery was occluded below the site of injection in order to prevent dilution of the medium. The lateral roentgenogram showed clearly the right vertebral and basilar arteries. Many small vessels over the cerebellum were visualized, and about 4 cm. of the proximal portion of the posterior cerebral arteries was seen clearly. The basilar artery and its branches were successfully demonstrated in a living human subject. There was no unpleasant reaction. It is suggested that the procedure be considered in cases in which the differential diagnosis includes aneurysm or defect of these vessels.

PRICE, Philadelphia.

THE CONNECTIONS OF THE BASAL OPTIC ROOT (POSTERIOR ACCESSORY OPTIC TRACT) AND ITS NUCLEUS IN VARIOUS MAMMALS. LOIS A. GILLILAN, J. Comp. Neurol. **74**:367 (June) 1941.

Serial sections of normal brains of various mammals were available for this study. Representative forms of Chiroptera, Insectivora, Rodentia, Carnivora, Ungulata and Primates were studied. For experimental material eyes were enucleated from the bat, rat and cat. Time was allowed for degeneration of the optic tract, and then the brains were removed and prepared serially. The nucleus tracti optici basalis was present in all forms studied. The principal afferent system to the nucleus was the tractus opticus basalis, a bundle of fibers which originated in the retina. The efferent fibers were distributed to various nuclei of the midbrain, including the substantia nigra, the lateral reticular gray substance and the oculomotor nucleus. A few of the primary neurons also reached these nuclei and, in addition, the fibrous capsule of the nucleus interpeduncularis. Both primary and secondary neurons crossed the midline in the supramamillary decussation. An anterior accessory optic tract was identified in the rodents and lower forms. This tract originated in the retina and terminated in the ventral and mediolateral portions of the nucleus subthalamicus. The author suggests that these accessory optic pathways are used for visual reflexes which are made quickly to fairly indistinct objects.

ADDISON, Philadelphia.

CEREBRAL CORTICAL STIMULATION OF GOATS, NORMAL AND NERVOUS. SAM L. CLARK, JAMES W. WARD and IRVING S. DRIBBEN, J. Comp. Neurol. **74**:409 (June) 1941.

Clark and his associates determined the motor area of the brain of the goat by electrical exploration and implanted electrodes. The motor area resembled that of the sheep brain except that the area for the movements of the hindlimb was medial to that for the forelimb and was anterior to the splenial sulcus, instead of behind it. Limb movements obtained from cortical stimulation were predominantly contralateral, and movements of parts involving muscles of both sides, such as chewing, showed unilateral dominance. Ear movements were obtained from stimulation of the ectosylvian gyrus, which lies outside the motor area. Little difference in response was obtained between normal goats and animals of a nervous breed found in middle Tennessee, previously studied by Clark and described as myotonic. Experiments with implanted electrodes showed that smaller subdivisions of the motor area were associated with specific movements.

FRASER, Philadelphia.

THE SURGICAL ANATOMY OF THE SUPERIOR HYPOGASTRIC PLEXUS. B. BERNARD WEINSTEIN, Surg., Gynec. & Obst. **74**:245 (Feb.) 1942.

Extirpation of the superior hypogastric plexus has been adopted for relief of the pain of carcinoma of the pelvic viscera, primary dysmenorrhea, cord bladder, cystalgia, Hirschsprung's disease, pruritus vulvae, vaginismus and other conditions.

Weinstein dissected 150 specimens, including 10 from infants, but gave particular attention to the female specimens. His observations indicate that the superior hypogastric plexus is a downward continuation of the intermesenteric nerve and is connected with the celiac plexus and the lumbar sympathetic ganglia. The intermesenteric nerves are composed of parallel fibers on the two sides of the aorta and arise from the renal or the aorticorenal ganglion, the periarterial plexus of the adrenal artery and the transverse aortic bar and the first and second lumbar sympathetic ganglia. The plexus is connected above with the inferior mesenteric periarterial plexus. The fibers may run downward to join the plexus directly or may join the intermesenteric nerves.

The superior hypogastric plexus receives fibers from each of the lumbar sympathetic ganglia, though the contribution of the ganglion is more marked, while branches from the inferior lumbar ganglia usually enter directly into the superior hypogastric plexus. The sacral ganglia do not usually contribute fibers to the superior hypogastric plexus, though in 6 per cent of cases the first sacral root may supply the plexus.

The larger portion of the fibers of the plexus diverge toward the lateral aspect of the trigone to terminate in the paired inferior hypogastric nerves. The chief innervation of the ureter is derived from these nerves. The inferior hypogastric nerves enter the uterosacral ligaments and course to the rectal ampulla, terminating in the plexus of Frankenhauser.

The sensory fibers of all the pelvic viscera traverse the superior hypogastric plexus with the exception of the fibers of the ovary and some fibers of the fallopian tube which have no connection by way of the superior hypogastric plexus nor do they traverse the inferior mesenteric ganglia or the aortic plexus. This observation should halt attempts to relieve pain by superior hypogastric sympathectomy. The afferent nerves from the ovary are in the periarterial ovarian plexus and reach the tenth thoracic level of the spinal cord. The afferent fibers from the uterus reach the cord through the superior hypogastric plexus at the level of the first lumbar to the tenth thoracic segment.

In only 2 per cent of dissections did the intermesenteric nerves fuse to form a single cord, known as the presacral nerve. In 29 per cent the nerves fuse on entering the trigone and immediately bifurcate, while in 35 per cent there is a wide triangular pattern of fibers. In only 8 per cent are the fibers shifted to the left, as has been reported.

GOTTEN, Memphis, Tenn.

Physiology and Biochemistry

STUDIES OF THE B VITAMINS IN THE HUMAN SUBJECT: V. THE NORMAL REQUIREMENT FOR THIAMINE; SOME FACTORS INFLUENCING ITS UTILIZATION AND EXCRETION. K. O'SHEA ELSOM, JOHN G. REINHOLD, JOSEPH T. L. NICHOLSON and CHARLOTTE CHORNOCK, Am. J. M. Sc. **203**:569 (April) 1942.

Elsom, Reinhold, Nicholson and Chornock carried out observations to determine whether the minimal requirement for thiamine is accurately expressed by the Cowgill formula and to evaluate in a preliminary fashion the role of body weight and of caloric intake in determining that requirement. Six women, without complicating disease, served voluntarily as subjects for the study. They resided in the vitamin ward of the Philadelphia General Hospital, where they consumed a constant daily quantity of an experimental diet for twenty-eight to one hundred and twenty days. A second group of 3 women, likewise resident in the vitamin ward, consumed essentially the same foods but in amounts which supplied approximately one half of their requirement.

The thiamine content of both food and urine was determined by an adaptation of the thiochrome method of Hennessy and Cerecedo. For the 6 women receiving approximately the required amount of thiamine as calculated by the Cowgill formula, $\frac{\text{thiamine (micrograms)}}{\text{calories}} = 0.0000284 \text{ weight (grams)} \times 0.166$, the ratio of thiamine to thiamine requirement varied from 1.03 to 1.1. In 3 subjects clinical manifestations of deficiency developed, whereas during the same period the other 3 subjects remained well, indicating that body weight may be disproportionately represented in the formula. The amount of thiamine excreted varied appreciably from day to day, independently of the volume of urine. The daily variations in excretion did not represent true differences in utilization but were related to factors governing the absorption or excretion of the vitamin. The output of thiamine varied directly with the intake and was independent of body weight in all of the subjects studied. The 3 subjects who subsisted at one half of their theoretic requirement of thiamine first showed the characteristic manifestations of deficiency on the twenty-third, thirty-second and forty-first day, respectively, after beginning the diet. The excretion of thiamine appears to be influenced mainly by factors which determine its concentration in the blood and tissues (daily intake, infection, proportion of dietary elements) rather than by the altered function resulting from its reduction in the diet.

MICHAELS, Boston.

BRAIN METABOLISM: VIII. THE EFFECTS OF ELECTRIC SHOCK AND SOME NEWER DRUGS. S. BERNARD WORTIS, DONALD SHASKAN, DAVID IMPASTATO and RENATO ALMANSI, Am. J. Psychiat. **98**:354 (Nov.) 1941.

Wortis, Shaskan, Impastato and Almansi studied the effects of drugs on cerebral metabolism by two methods: The first consisted of injecting the drug in specified concentration into a white rat and after fifteen minutes removing the cerebral cortex, mincing it and studying respiration by the Barcroft-Warburg method for two hours. In the second method the cortex of a normal rat was immersed in Ringer's phosphate substrate both with and without dextrose and containing the drug in a specified concentration and the oxygen consumption measured. The drugs studied consisted of acetylbetamethylcholine, epinephrine, physostigmine, morphine, picrotoxin, pilocarpine, prostigmine, tyramine, caffeine, cocaine, ergot, ergotoxine and nicotine. The injected drugs failed to affect the oxygen consumption of the brain in the dextrose substrate, but tyramine, picrotoxin and prostigmine stimulated oxygen consumption in the sugar-free substrate. In the immersion experiment, epinephrine, caffeine, cocaine, ergotamine and ergotoxine inhibited the oxygen consumption in both the dextrose and the sugar-free substrate.

The authors studied the effects of electrically induced convulsions on brain metabolism by two methods: The first consisted of administering a single convulsive shock to a rat while the animal was still in coma, removing the brain and studying the respiration. This method showed that the total brain respiration is depressed in electrically convulsed animals. By the second method the authors induced a total of nine to fifteen convulsions in rats at a rate of two shocks per week. From three to thirty days after the last convulsion the brains were removed and studied in like manner. Again, the authors found that the metabolism of the brain was depressed in both the plain and the dextrose substrate, the depression being greater after repeated than after single shocks. Comparison of the effects of various forms of shock therapy on oxygen utilization by the brain tissue reveals that metrazol and camphor increase the respiratory metabolism of the tissue while electric convulsions interfere with brain respiration. Insulin interferes with cerebral respiration to a greater extent than does electric shock, the effect being due in a large part to the lack of dextrose.

FORSTER, Boston.

THE PHOSPHORUS METABOLISM OF THE BRAIN AS MEASURED WITH RADIOACTIVE PHOSPHORUS. B. A. FRIES and I. L. CHAIKOFF, J. Biol. Chem. **141**:479, 1941.

In general it appears that the turnover of phosphatide in the brain is slow. Fries and Chaikoff have studied the metabolism of phosphorus in the brain using radioactive p^{32}. The recovery of total radioactive phosphorus in the forebrain, cerebellum, medulla and spinal cord was compared at twenty-four and forty-eight hours after the administration of p^{32}. The highest recovery of p^{32} in all divisions of the central nervous system was found on the day of birth. From birth until the time the rat attained a weight of 50 Gm. a rapid decline in recovery of p^{32} was observed throughout the brain. As growth proceeded beyond 50 Gm. the decline continued, but at a much slower rate. The recovery of p^{32} was not uniform throughout the central nervous system. From birth until the time the rat attained a weight of 50 Gm., it was highest in the spinal cord or the cerebellum. After this the relative activities of forebrain, cerebellum and medulla rose steadily, and by the time a weight of 200 or 300 Gm. was reached the recoveries in the cerebellum, medulla and forebrain exceeded the recovery in the cord. The labeled phosphorus present as phosphatide did not account for more than 20 to 30 per cent of the total labeled phosphorus deposited in the brain.

PAGE, Indianapolis.

STUDIES ON MANGANESE DEFICIENCY IN THE RAT. P. D. BOYER, J. H. SHAW and P. H. PHILLIPS, J. Biol. Chem. **143**:417, 1942.

Pronounced manganese deficiency in the rat has been produced by use of animals weaned without access to manganese. This deficiency resulted in definitely impaired growth in both the male and the female rat. In the manganese-deficient female rat estrous cycles were irregular or absent, and there was a marked delay in the opening of the vaginal orifice. Manganese deficiency in the male rat caused testicular degeneration and complete sterility, due to lack of production of spermatozoa. Both male and female manganese-deficient rats were unable to reproduce. No histologic abnormalities were detected in the adrenals, kidneys, pituitary gland or thyroid of the manganese-deficient rat. The deficiency did not result in a reduced ascorbic acid content of tissues, nor did ascorbic acid stimulate growth. Synthesis of ascorbic acid from mannose by rat liver and other tissues in vitro with and without added manganese could not be obtained. The arginase concentration in the liver of the manganese-deficient rat was reduced. There were no essential differences in the activity of the intestinal dipeptidases studied.

PAGE, Indianapolis.

CEREBELLAR ACTION POTENTIALS IN RESPONSE TO STIMULATION OF THE CEREBRAL CORTEX IN MONKEYS AND CATS. ROBERT S. DOW, J. Neurophysiol. **5**:121, 1942.

Single shocks with a peak of 140 volts were delivered to various areas of the cerebral cortex in 8 monkeys and 11 cats, and the corresponding reactions in different parts of the cerebellum were amplified and recorded.

The most pronounced responses were contralateral, though homolateral ones were observed. Stimulation of a single point on the cerebral cortex could result in action potentials in all cerebellar lobes which received pontocerebellar connections.

Responses in the cat indicated that no topographic or cytoarchitectonic subdivision of the cortex was represented predominantly in any cerebellar lobe.

Differences in amplitude and threshold of responses in the monkey pointed to some correlations as probably significant. These correlations were more evident in the case of cytoarchitectonic than of topographic areas in the cortex. Projections from the precentral and postcentral gyri seemed greatest to the vermian and paravermian lobules. There was a tendency for the face area to be best

represented in the rostral lobes (culmen) and for the leg area apparently to send projections chiefly to the caudal lobules (paramedian and pyramidal).

DRAYER, Philadelphia.

SOME PHYSIOLOGICAL ASPECTS OF AUDIOGENIC SEIZURES IN RATS. DONALD B. LINDSLEY, FRANK W. FINGER and CHARLES E. HENRY, J. Neurophysiol. **5**:185, 1942.

The production of convulsive seizures in rats by high-pitched sounds has been utilized in the study of the electroencephalographic and electrocardiographic changes which accompany convulsive phenomena. Two underlying processes were noted: (1) an autonomic discharge, evidenced by changes, generally an increase, in heart rate, and (2) an electrocortical discharge, shown by the convulsive-like patterns of the electroencephalogram at the beginning of the attack. The second process did not always follow the first, but in such cases the animals showed "substitute behavior" (nose rubbing, teeth chattering, etc.).

Restraint of the animals mechanically, curarization and bilateral vagotomy all were effective preventives of seizures. The authors believe that the last two procedures acted to curtail sensory reenforcement of the central excitatory state of the cortex. Curare blocks effective autonomic and somatic responses from which the sensations arise, and much of the sensory influx from peripheral autonomic activity would be blocked by vagotomy. The outlet provided by the initial struggle against restraint is a possible explanation for the prevention of seizures by this procedure.

DRAYER, Philadelphia.

EFFECT OF ESERINE [PHYSOSTIGMINE] ON NEUROMUSCULAR TRANSMISSION. JOHN C. ECCLES, BERNHARD KATZ and STEPHEN W. KUFFLER, J. Neurophysiol. **5**:211, 1942.

Circulation-intact nerve-muscle preparations from cats and isolated nerve-muscle preparations from frogs were used for most of the studies. A few observations were made on single nerve-muscle fibers from frogs.

In both cat and frog preparations, physostigmine increased and lengthened the local negative potential change (end plate potential) set up by one or more nerve volleys at the myoneural junction and also produced a delayed wave (with a height up to 40 per cent of the spike and a duration of several seconds) after repetitive volleys. Curare counteracted the effect of physostigmine to some degree, but even in fully curarized muscles there was prolongation of the end plate potential with physostigmine.

Physostigmine lengthened the action of the neuromuscular transmitter. The prolonged junctional negativity resulted in catelectrotonic effects, such as repetitive muscle spikes, when above threshold size, and lengthening of the refractive period. Retrograde propagation of impulses from muscle to nerve was observed in the cat preparations during the prolonged physostigmine potentials.

An effort was made to analyze the curare-physostigmine antagonism. It was found that curare did not prevent the inhibition of cholinesterase by physostigmine and that it had little, if any, effect in quickening the adaptation of muscle to acetylcholine.

The authors conclude that by making certain plausible assumptions, they can reconcile the observed actions of physostigmine and curare with the hypothesis that acetylcholine is responsible for all the local potential changes set up by nerve impulses.

DRAYER, Philadelphia.

EXCITABILITY OF CEREBRAL CORTEX IN INFANT MACACA MULATTA. MARGARET A. KENNARD and W. S. MCCULLOCH, J. Neurophysiol. **5**:231, 1942.

Facilitation, extinction and suppression of motor response to cortical stimulation were observed in a monkey 20 days old. The movements produced were

contralateral, and they were elicited only when stimuli were delivered to area 4. No responses were obtained from area 6 or from the postcentral convolution. Facilitation and extinction of motor responses were demonstrated easily. Relatively high voltages were required for successful stimulation, and responses were less prompt and discrete than in the adult. No responses could be obtained in the leg, and the hand was less easily stimulated than the face.

Lack of response from area 6 is in agreement with the fact that forced grasping is normal at this age.

Although removal of area 4-s fails to produce spasticity in monkeys of this age, stimulation of this area suppressed motor responses. Therefore, it is apparent that some mechanism other than simple release of cortical activity in area 4 must be necessary to produce the spasticity observed in older animals after the removal of area 4-s.

DRAYER, Philadelphia.

EFFECTS OF PRESYNAPTIC VOLLEYS ON SPREAD OF IMPULSES OVER THE SOMA OF THE MOTONEURON. BIRDSEY RENSHAW, J. Neurophysiol. **5**:235, 1942.

Decerebrated or lightly anesthetized cats and rabbits were subjected to laminectomy. A microelectrode was inserted into the ventral horn. Differences in potentials between this electrode and an indifferent one were recorded when centripetal stimuli of various types were initiated.

A centripetal impulse over the ventral root produced a short initial positive change in potential in the ventral horn followed by a negative deflection, which lasted one to two milliseconds. There was a final smaller, but prolonged, positive phase. Repetitive volleys produced negative deflections of diminishing size. Dorsal root volleys altered these ventral horn responses to ventral root impulses. Factors influencing the result were the conditioning dorsal root fibers, the motoneurons tested and the interval between the arrival at the cord of the conditioning and of the testing volley. Retrograde conduction in the motoneurons occurred with a decrement. Activity in the sensory and premotor neurons could augment or decrease the penetration of the impulse into the cell body and dendrites of the motoneuron.

DRAYER, Philadelphia.

Diseases of the Brain

FATAL HYPERINSULINISM WITH CEREBRAL LESIONS DUE TO PANCREATIC ADENOMA. A. J. KERWIN, Am. J. M. Sc. **203**:363 (March) 1942.

Kerwin reports the case of a married woman aged 42. She had been well until Aug. 3, 1940, when she became mentally confused and wandered aimlessly about the house. On the morning of August 9 she was found in a comatose condition, from which she did not recover. Examination revealed only weakness of the right lower part of the face. She roused somewhat, and her speech was thick and blurred. On August 13 she was hospitalized, after having been in deep coma for the previous day and a half. A provisional diagnosis of hypoglycemia was made, the blood sugar being 43 mg. per hundred cubic centimeters. Up to this time the diagnosis of pancreatic adenoma with hyperinsulinism had been considered likely, but inasmuch as intravenous injection of dextrose failed to rouse her from coma, the diagnosis was abandoned in preference for that of an unusual form of encephalitis. She died sixteen days after the beginning of her illness. Autopsy revealed a small spherical nodule in the tail of the pancreas, 3 cm. from the end. The insulin content of this tumor was 30 units per gram of tissue. The tumor was composed of epithelial cells arranged in slender ribbons, rounded masses and alveolar structures. The brain showed congestion of the superior cerebral veins and a small quantity of fresh blood in the subarachnoid space over the right frontal lobe. Edema was pronounced in both the gray and the white matter, and there was considerable swelling of the oligodendroglia. There were some degeneration of nerve cells and neuronophagia. The midbrain presented moderate

subependymal gliosis below the aqueduct. The case was notable for the rapidly fatal issue and the fact that the diagnosis was missed because the patient did not respond to the administration of dextrose. The rapid progress of the disease would seem to account for the lack of striking changes in the brain.

MICHAELS, Boston.

NARCOLEPSY. WILLIAM F. MURPHY, Am. J. Psychiat. **98**:334 (Nov.) 1941.

Murphy reported 7 cases of narcolepsy, which he divided into five groups. The first group included 2 cases in which no organic or psychopathic background was demonstrable. The second group consisted of 2 cases which followed encephalitis. In the first case frank encephalitis, associated with parkinsonism and cataplexy, occurred four years before the onset of the narcolepsy. In the second case the evidence for encephalitis was not clearcut. The third group was comprised of 1 case of narcolepsy due to thyroid disturbance, which was remedied by iodine medication. One case in which there was a psychopathologic background comprised the fourth group. The fifth group, that of cataplexy without narcolepsy, consisted of 1 case. Murphy concludes that narcolepsy is the borderline syndrome common to cases both of functional and of organic disease of the brain. He considers the narcoleptic attacks to be of the nature of a release phenomenon in that, owing to cortical control being held in abeyance, the normal adult monophasic sleep becomes polyphasic, and thus more primitive.

FORSTER, Boston.

CONCERNING TRANSFER OF CEREBRAL DOMINANCE IN THE FUNCTION OF SPEECH. WILLIAM NEEDLES, J. Nerv. & Ment. Dis. **95**:270 (March) 1942.

Needles discusses the ability of one cerebral hemisphere to take over the language function of the other after the latter has been damaged. He reviews 4 cases described by different authors in which the following common factors were present: (1) loss of function in the right hand; (2) adoption of function by the left hand, and (3) years later, onset of aphasia.

In the first 2 cases cited the patients had originally been right handed; some years after the loss of function of the right hand and the development of left handedness, each had become aphasic subsequent to a lesion of the right hemisphere. The third and fourth cases concerned persons who from early life had been unable to use the right hand but in both of whom transient aphasic states developed after operation on the left hemisphere.

The explanation is proposed that in these cases the function of speech is not shifted from one hemisphere to the other but continues to be participated in by both hemispheres. This is also probably true in cases of ambidextrous persons and of children.

The last 2 cases cited adduce evidence to support the belief that hemispheric dominance is predestined rather than dependent on the previous function of the contralateral hand, while the first 2 cases indicate that a speech center can be secondarily set up.

The phenomenon of crossed aphasia indicates that in some cases the center for the preferred hand and the center for speech lie in opposite hemispheres. The concept of stock handedness as advanced by Kennedy may explain some such instances but leaves others unanswered.

The suggestion is made finally that in cases of aphasia with hemiplegia training of the contralateral hand may stimulate reeducation of the intact cerebral hemisphere.

CHODOFF, Washington, D. C.

MULTIPLE MYELOMA. RALPH K. GHORMLEY, GEORGE A. POLLOCK, BYRON E. HALL and LAWRENCE H. BEIZER, Surg., Gynec. & Obst. **74**:242 (Feb.) 1942.

The authors bring up to date a previous study of multiple myeloma. Forty-one additional patients have been examined in the last three years, making a total of 127 patients studied in the sixteen years from 1924 to 1939 inclusive. Multiple

myeloma is a highly malignant tumor of the bone marrow occurring after the fifth decade of life. The cause is unknown; men are affected twice as frequently as women, and trauma is not a factor. Microscopically, the tumor is made up predominantly of plasma-like cells, and normal myeloid tissue and fat spaces are absent. The cells differ from normal plasma cells; they are now called myeloma cells and seem to be derived from the reticuloendothelium.

There is no clinical picture pathognomonic of the disease. The average duration of symptoms was one year; backache was the chief complaint and loss of strength and weakness the next most common symptom. Albuminuria was present in 70 per cent of the patients, and some patients had been treated for nephritis. Bence Jones bodies were present in 60.7 per cent. The diagnosis is based on the alterations in the chemical constituents of the blood, the roentgenographic changes and aspiration of sternal marrow. The prognosis is poor; the duration of life after diagnosis in this series was one year.

GOTTEN, Memphis, Tenn.

DISTURBANCES OF OCULAR MOVEMENTS WITH PSEUDOHEMIANOPSIA IN FRONTAL LOBE TUMORS. J. SILBERPFENNIG, Confinia neurol. **4**:1, 1941.

Silberpfennig describes 2 cases of tumor of the frontal lobe, in each of which a pseudohemianopsic disturbance was observed. In the first case there was a glioma of the right frontal lobe, with a second, smaller tumor located in the upper wall of the posterior horn of the left lateral ventricle; disturbance in the perception of objects to the left of the midline was present, but no true hemianopsia. In the second case the patient also exhibited a tendency to ignore objects to the left but had had no hemianopsia; in this patient a meningioma compressed the first and second frontal convolution on the right, with some involvement of the parietal lobe. In both cases the eyes were deviated to the right and gaze to the left of the midline was impaired. In both cases lack of visual attention to the left was manifested. Both gaze and visual attention could be temporarily improved by increase in general attention, stimulation of visual attention and vestibular stimulation.

DEJONG, Ann Arbor, Mich.

PROGRESSIVE SYNDROME CONSISTING OF SYMMETRIC CUTANEOUS AND CONJUNCTIVAL TELANGIECTASES AND CEREBELLAR MANIFESTATIONS. LOUIS-BAR, Confinia neurol. **4**:32, 1941.

Louis-Bar reports the case of a child aged 9 who had a cerebellar syndrome and cutaneous manifestations, both of which had progressively developed from the age of 3 years. The manifestations of involvement of the nervous system consisted of ataxia, disturbance of speech and intellectual retardation. The skin showed telangiectatic areas and café au lait spots of fernlike distribution, and there were symmetric conjunctival capillary telangiectases.

DEJONG, Ann Arbor, Mich.

SYMPTOMATOLOGY AND MORPHOLOGY OF CEREBRAL HEMANGIOMA CAVERNOSUM. I. FARAGÓ, Confinia neurol. **4**:42, 1941.

Faragó reports 2 cases of cerebral hemangioma. The first was that of a woman aged 30 who had convulsions and died after her first delivery. Postmortem examination showed hemangioma cavernosum of the right cerebral hemisphere. The tumor contained a thrombus and showed evidence of previous hemorrhages. The second case was that of a man aged 59 who died after the onset of left hemiplegia. In this case there was also hemangioma cavernosum with evidence of previous hemorrhages. The author believes the sudden manifestation of neurologic symptoms to to be due to thrombosis within the tumor. As a result of this there is alteration in the consistency and volume of the tumor, with changes in cerebral circulation and intracranial pressure.

DEJONG, Ann Arbor, Mich.

OPHTHALMOPLEGIC MIGRAINE. E. BÜRKI, Confinia neurol. **4**:54, 1941.

On the basis of a report of 8 cases and a review of the cases recorded during the past twenty years, Bürki concludes that it is possible to distinguish two forms of ophthalmoplegic migraine. The essential, or genuine, form appears in youth, is recurrent and decreases in severity with advancing age; the prognosis is not necessarily poor, although permanent paresis may remain in cases of frequent recurrence. The symptomatic form is secondary to organic changes at the base of the skull, especially aneurysm. This form may begin in advanced age, and the prognosis is less good, especially as permanent paralysis may develop.

The term ophthalmoplegic migraine may be used for every variety of ocular palsy accompanying one-sided headache. Recurrent oculomotor paralysis is probably a special form of essential ophthalmoplegic migraine.

DEJONG, Ann Arbor, Mich.

Peripheral and Cranial Nerves

INJURY TO THE SPINAL CORD AND SPINAL NERVE ROOTS IN THE COURSE OF PARAVERTEBRAL INJECTION. CLARENCE W. OLSEN, Bull. Los Angeles Neurol. Soc. **6**:131 (Sept.) 1941.

Olsen examined a woman aged 55 who had been given paravertebral injections between the left scapula and the spine when she was 37 years old. During the third injection she experienced severe local pain and became numb and weak in the left lower extremity. She had a sensation of stiffness about the lower part of the thorax and walked only with great difficulty. She improved slowly, but when examined eighteen years later she had a partial Brown-Séquard syndrome, with both motor and sensory changes. Olsen cites a similar case from the literature in which the cervical portion of the spinal cord was injured during paravertebral block anesthesia for thyroidectomy. It is his opinion that injury to the spinal cord can occur in such cases by direct traumatization by the needle, by hemorrhage due to a damaged blood vessel or by injection into a blood vessel, the subarachnoid space or in the spinal cord itself.

MACKAY, Chicago.

ALCOHOLIC NEUROPATHY WITH MULTIPLE SCLEROSIS. SERGE ANDROP, J. Nerv. & Ment. Dis. **93**:333 (March) 1941.

Androp describes the case of a man aged 47, an alcohol addict for twenty-five years, who had had frequent attacks of neuritis and delirium tremens and had drunk as much as a quart (946 cm.) of gin daily. There were tremors, loss of weight, weakness of the legs and myocardial insufficiency. He was excited and delusional, with marked tenderness of nerve trunks, difficulty in locomotion and a positive Romberg sign. He improved for a time under medication with vitamin B_1 but later became unable to stand, with hyperactivity of tendon reflexes except for absence of the left knee jerk. The abdominal reflexes were unequal on the two sides. Generalized convulsions, incontinence, weakness and incoordiation of the upper extremities followed and later decubitus ulcers and subicterus. The clinical diagnosis was chronic alcoholism with peripheral neuritis. Pathologic study revealed disseminated plaques of demyelination and gliosis in the white matter of the brain and spinal cord. In some areas the axis-cylinders were nearly destroyed and in others partly preserved. Dilatation of smaller blood vessels and proliferation of capillaries were seen, with perivascular collections of lymphocytes and plasma cells. Gliosis was moderate. Mild degenerative changes were seen in the cortical ganglion cells. Androp leaves unanswered the question whether two diseases coexisted or whether only one disease, due to toxic factors or vitamin deficiency, was present. He classifies the condition as encephalomyelopathy with chronic, disseminated demyelination, a variety of multiple sclerosis.

MACKAY, Chicago.

PHANTOM LIMBS AND BODY SHAPE. GEORGE RIDDOCH, Brain **64**:197, 1941.

The condition of fantom limb, which follows a lesion of sensory paths, is not the outcome of gross mental disturbance but is determined by an upset in physiologic processes, and its explanation must be searched for on that basis. It occurs most commonly after amputation, but a similar condition is also observed with lesions of the peripheral nerves and plexus, with injury to the spinal cord, and, finally, with jacksonian seizures.

After amputation the extent of the fantom limb tends to recede with time. Recession is delayed, however, by the use of an artificial limb, by faradization of the stump or by the presence of pain.

Pain in the fantom limb is common as a continuation of preamputation pain. When pain has been present in the injured part for some time prior to operation, a painful fantom limb can almost certainly be predicted. It occurs also when the stump is inflamed. Removal of a painful neuroma may give relief, but if inflammation has been long standing, even root section is ineffectual.

Painful fantom limb occurs even with a healthy stump. In this category amputation of the upper limb provides most examples, and constitutional, often inherited, defective resistance to pain and discomfort can usually be traced in the history.

Spinothalamic section relieves pain but must be sufficiently high to produce analgesia of a large area around the stump. Complete disappearance of fantom limb occurs only after removal of the area of representation in the cerebral cortex.

The observations in cases of fantom limb suggest that throughout life there is developed a schema of the body, built up by impulses from receptors in joints and tendons, by sensory impressions from the skin and, to a lesser extent, by visual observation. By means of perpetual alterations in position, there is being built up always a new model of oneself, which constantly changes.

After amputation the schema of the limb becomes "frozen" in the condition obtaining just prior to the injury. Persistence of paresthesia preserves the outline model of the fantom. The continuance of the fantom depends on the interaction of peripheral stimulation and central inhibition. MASLAND, Philadelphia.

A STUDY OF ERYTHROEDEMA POLYNEURITIS (PINK DISEASE). T. A. RATCLIFFE, J. Ment. Sc. **87**:545 (Oct.) 1941.

Ratcliffe reports 15 cases of pink disease; 6 of the patients were girls and 9 were boys. The author states that sex differences are probably of no etiologic significance. The age of onset varied from 3½ months to 1 year 5 months, and the mortality rate in his series was 13.3 per cent. It was impossible to trace a familial incidence. In many of the cases the onset of the disease appeared to be correlated with some other acute illness. Photophobia, anorexia, hypotonia and cutaneous rash were almost constant features, the rash being of less frequent occurrence than the others. Apart from hypotonia, neurologic symptoms were uncommon. In the patients personally examined by the author, the knee and biceps jerks were exceedingly difficult to elicit, but in no case were they absent. All of the bodily musculature was atonic, which may account for the sudden death from cardiac failure to which children with this disease are liable. Sensation was examined, so far as is possible in a baby, and there appeared to be diminution of sensibility for painful stimulation. The spinal fluid was examined in only 1 case and was found to be normal.

The psychologic state of the child is characterized by excessive irritability. For the most part the child lies curled up in the "knee-elbow" position, the face buried in the pillow. If disturbed, he will cry and withdraw from the examiner. Photophobia is usually noted. In a second type of the disease the child crawls about continually or rocks for hours or continuously performs acrobatic somersaults for a long time. In the rare type of the disease there is extreme lethargy, the child being miserable and irritable. This probably represents the advanced stage. No specific treatment for the disease is known, but particular attention is paid to dietetic measures.

It has been stated that the incidence of pink disease has been increasing in recent years, but this is probably more apparent than real. The question of etiology is still unanswered. One theory maintains the disease is due to a dietary deficiency, but the missing factor is unknown. It does not appear to be any of the known vitamins. A second theory postulates that the disease is caused by a specific organism or filtrable virus. No actual virus or organism has ever been isolated. Some attempts have been made to show that the disease is due to an endocrine disorder, but nothing definite is known about this factor. The prognosis should be guarded and the treatment directed toward combating the symptoms, particularly toward abolishing the irritability. BRACELAND, Chicago.

PUPILLARY CHANGES ASSOCIATED WITH NEURAL MUSCULAR ATROPHY: DEJERINE-SOTTAS DISEASE. ERNST STÖRRING, Ztschr. f. d. ges. Neurol. u. Psychiat. **171**:95 (Feb.) 1941.

Störring reports the case of a 32 year old man with a history of difficulty in walking since his tenth year. The illness progressed slowly so that the patient was unable to walk when he was 30. When he was 18 his pupillary reactions were noted as normal. At the age of 32 the neurologic picture was that of peripheral neuritis with motor and acral sensory impairment. Deep sensibility was impaired. The median nerves were thickened, and the ulnar nerves were hard and insensitive. There were no fibrillations. Pes cavus was present, with a mild tendency to main en griffe. Electrical stimulation gave diminished reactions to the faradic and galvanic currents, but there was no reaction of degeneration. The tendon reflexes, except for the biceps, were not elicited. Examinations of the blood and spinal fluid revealed nothing abnormal.

The pupils were generally in mid-dilatation, the left usually being wider. Frequent variation in their size was noted. These changes in size took place slowly and while the pupils were being studied. The left pupil was usually oval and eccentric, though at times it was round and eccentric. No pupillary reactions were noted with the usual direct and consensual light stimulation. Movements of the iris were not seen even with the slit lamp. When the pupils were stimulated by light for a relatively long time slow narrowing was noted. During convergence, after a short latent period, there was tonic narrowing. Dilatation of the pupils was also tonic. Dilatation occurred after the patient was kept in the dark for a long time. Light stimulation then caused slight tonic narrowing of the pupils. The reaction to cocaine and physostigmine was normal; after strychnine miosis came on faster during convergence, but there was no reaction to light.

These pupillary reactions conform to the pupillotonic type as described by Adie. Most of the descriptions of pupillary reactions in cases of Dejerine-Sottas disease are too inaccurate and incomplete to justify a conclusion regarding their nature. The case of Slauck is the only one in which the observations were recorded carefully enough to justify the diagnosis of a tonic pupil.

The author points out the importance of neurologic study of all cases of tonic pupils. He thinks that many of the disturbances called Adie's syndrome are really formes frustes of heredodegenerative disease, such as the Dejerine-Sottas syndrome. No explanation is given for the pupillary changes accompanying hypertrophic interstitial neuritis. The author doubts whether similar hypertrophic changes in the oculomotor nerves could account for the change. He also rejects the hypothesis of a hypothalamic disturbance. SAVITSKY, New York.

Treatment, Neurosurgery

ENCEPHALOPATHIA ALCOHOLICA. NORMAN JOLLIFFE and HERMAN WORTIS, Am. J. Psychiat. **98**:340 (Nov.) 1941.

Jolliffe and Wortis point out the importance of avitaminosis in alcoholism, as indicated by the deficient diet, by the impaired absorption and utilization and, finally, by the increased vitamin requirement, due to the increased total metabolism.

The authors include the psychoses of pellagra and the "encephalopathic syndrome" under symptoms resulting from a deficiency of nicotinic acid. The "encephalopathic syndrome" consists of clouding of consciousness, cogwheel rigidities of the extremities and uncontrollable sucking and grasping reflexes. Treatment of this group of psychoses with hydration and nicotinic acid has reduced the mortality to 15 per cent. The authors conclude that these symptoms are the result of the nicotinic acid deficiency.

In Wernicke's syndrome thiamine deficiency is considered responsible for the peripheral neuropathy and the ophthalmoplegia. The clouding of consciousness is not specific and may be related to a number of deficiency factors. Other deficiency syndromes may and do superimpose themselves on the usual picture. Jolliffe and Wortis conclude, therefore, that in this syndrome more than a simple thiamine deficiency is present but that the syndrome is invariably associated with the deficiency of thiamine. Treatment must consist, therefore, of a high calory, vitamin-rich diet, with administration of thiamine hydrochloride and other vitamin concentrates. Jolliffe and Wortis conclude that the role of thiamine in Korsakoff's syndrome, both as to genesis and as to treatment, remains to be determined. The authors believe that the deficiency of thiamine and nicotinic acid is not specific in delirium tremens but that it is of considerable importance in producing other types of nutritional encephalopathy; hence thiamine hydrochloride and nicotinic acid, as well as the entire vitamin B complex, should be given to all patients with delirium tremens in order to prevent the development of other deficiency syndromes. Jolliffe and Wortis stress the fact that the deficiency syndromes frequently merge into one another. Treatment must be instituted before irreversible changes are present. Since the deficiencies are usually multiple, a well balanced diet, in addition to specific vitamin therapy, is indicated. FORSTER, Boston.

FOLLOW-UP RESULTS IN INSULIN SHOCK THERAPY AFTER ONE TO THREE YEARS. T. D. RIVERS and E. D. BOND, Am. J. Psychiat. **98**:382 (Nov.) 1941.

Rivers and Bond report the results of insulin treatment of 154 patients with schizophrenia. The results were so divergent as to permit division of the patients into two groups. The first of these comprised 82 patients treated from 1936 to 1938 by a relatively mild form of insulin shock and at the hands of different physicians. The second group, consisting of 72 patients, was treated in 1939 and 1940 by one physician and with a more severe form of shock. Of the first group of 82 patients, 44 per cent were greatly improved at the end of therapy, and two years later 32 per cent of 76 patients were still decidedly improved. However, in the second group, those treated in 1939 and 1940, 63 per cent of 71 patients were greatly improved at the end of treatment, and two years later, 61 per cent of 18 patients had maintained this degree of improvement. A compilation of results over a total of four years showed that 53 per cent of 154 patients were decidedly improved at the end of treatment but that at the end of four years only 17 per cent of 23 patients had maintained improvement. Rivers and Bond point out that in the same hospital the spontaneous rate of improvement at the end of five years was 10 to 20 per cent. Comparison of the four year record with the spontaneous recovery rate indicates that the end results are not altered by insulin therapy. The factors, however, which modify the statement are (1) the shorter duration of the illness as a result of insulin therapy, (2) the weighting of the group reported on by the inclusion of cases of long-standing illness and (3) the inadequate treatment given some of the patients (1936 to 1938 group).

FORSTER, Boston.

ROENTGEN THERAPY OF ONE HUNDRED CONSECUTIVE TUMORS OF THE BRAIN OR SPINAL CORD. F. B. MANDEVILLE, D. A. RUSSELL and MAUDE S. FARLEY, Radiology **47**:560 (Nov.) 1941.

Mandeville, Russell and Farley treated 100 patients with tumor of the brain or spinal cord with roentgen radiation during the last six years. The technic used is as follows: 200 kilovolts, with a half-value layer of 0.8 to 2.0 mm. of

copper, an effective wavelength of 0.16 to 0.12 angstrom unit, a skin-target distance of 50 cm. and large daily total doses of 400 to 800 r, measured in air. Usually 500 r is given to a single portal, or 250 r to two portals. It is customary to direct radiation through four portals 10 cm. in diameter to the skull or through two posterior oblique portals to the spine. In this series each portal received a total dose of from 700 to 1,200 r; occasionally 1,800 r was given with smaller portals in cases of tumor of the pituitary gland or spinal cord. Treatment may be completed in five days, although a therapeutic period of several weeks is preferred. A second series is given in six weeks and three more series at three month intervals.

Few patients cooperate with this plan of treatment; hence an attempt is made to prolong the first series and to raise the tumor dose, but never above 3,000 r. Recently the authors have used 400 kilovolts, with a half-value layer of 4.4 mm. of copper and a skin-target distance of 170 cm., a low intensity (measured in roentgens per minute) and doses of 200 r. As much as 5,400 r on the skin through one portal has been given in this manner over a forty day period. This type of therapy is felt to be preferable, as it gives a more adequate tumor dosage.

Preirradiation and postirradiation specimens were not available in this series, as in only 4 of 34 cases of death was permission for autopsy obtained, 16 patients could not be traced and 50 are still living.

The authors treated 76 patients with tumor of the brain.

In the group with medulloblastoma, 11 were males and 1 was a female, and all the tumors were cerebellar. The ages of the patients ranged from 3 to 40 years. Ten patients were followed; 5 are living and 5 are dead. Two patients, each of whom lived four years and five months, died with metastases to the spinal cord. Fifteen authors have concluded that this lesion is radiosensitive; only two mentioned it as radioresistant. Most authors advise radiation therapy as an adjunct to the treatment. As this tumor may spread through the subarachnoid pathways and implant itself anywhere in the cerebrospinal axis, roentgen therapy was given through four skull portals and through posterior portals over the spinal cord. None of the patients received the full five series, and of the 5 now living, only those who have received more than 3,000 r can hope for any prolongation of life. The entire cerebrospinal axis should be irradiated, and only relatively large tumor doses seem to have any beneficial effect.

In the group with glioblastoma multiforme, 4 were females and 4 males, the ages ranging from 11 to 65 years. Eight patients were followed, 1 of them by examination of preirradiation and postirradiation specimens. In this case tumor cells were found, even though a dose of 3,172 r had been given in one series. The results have been poor for this group of patients, only 2 of the 8 being alive. Large doses over prolonged periods may be beneficial.

Five of the patients with pontile tumors were males and 5 females. The ages ranged from 3 to 48 years. All responded poorly to treatment, 6 of the 10 dying in a very short time.

Two patients with astroblastoma were seen; both are doing well, one four years and six months after a tumor dose of 2,000 r and the other two years and six months after a series of treatments with a total dose of 3,412 r. The authors believe that it is advisable to irradiate astroblastoma.

Five patients with astrocytoma were treated—3 females and 2 males. The ages ranged from 6 to 33 years. One patient was not traced; the others are living and well, but the authors feel that the doses given were too small to justify attributing beneficial effects to irradiation.

A group of 4 patients with ependymoma which had been incompletely removed at operation were treated; all are living and well. Despite the divergence of opinion as to whether these tumors should receive radiation, the authors believe it wise to give this therapy because of the possibility of development of these relatively benign tumors into malignant growths.

Eight patients with craniopharyngioma were treated, and 7 are alive and well. Treatment of this tumor is advised on the assumption that irradiation may help to destroy or inactivate the epithelial cells lining the cyst wall after evacuation of the cyst.

Eight patients with pituitary adenoma were treated, 4 of them being alive one and a fourth, three and a half, seven and eleven years after treatment. Roentgen therapy is reserved as a postoperative measure for those patients who refuse operation. The chromophile type of pituitary adenoma is more radiosensitive than the chromophobe type.

Ten patients had brain tumors which were unclassified, and 7 of these have been traced. Two patients with cerebellar tumor (probably medulloblastoma) lived three and a fourth years each after receiving a dose of 3,200 r. One patient with a tumor of the pineal gland is living after five years. A patient with tumor of the right frontal lobe, probably a cerebral astrocytoma, lived one year after four series of treatments, with a dose of 5,935 r.

Only 1 patient with spongioblastoma polare was treated after partial excision of the tumor. A dose of 1,435 r was given, the patient living only ten months.

One patient with an incompletely removed cerebellar hemangioblastoma was treated with a tumor dose of 1,626 r and lived a little over a year.

Five patients with hemangioma were treated. The results have been unimpressive. Meningioma is not customarily treated, but the authors feel that it is wise to treat such a tumor after it has been incompletely removed. Sarcoma should be treated like the meningioma. Two patients with reticulum cell sarcoma have received radiation; this tumor is radioresistant.

Four patients with metastatic tumors were treated; all are dead. Roentgen therapy for these patients is not advised unless the primary site is not found.

Sixteen patients with tumor of the spinal cord have been treated, intensively whenever possible. Four had hemangioma, 2 glioblastoma multiforme, 1 medulloblastoma, 2 metastatic tumors and 7 a tumor which was unclassified except as intramedullary glioma.

The authors conclude that improvement or prolongation of life has been secured by the irradiation of tumors of the brain and spinal cord in patients who have cooperated at least partially in the treatment.

KENNEDY, Philadelphia.

Encephalography, Ventriculography, Roentgenography

CONGENITAL DEFORMITIES IN THE REGION OF THE FORAMEN MAGNUM; BASILAR IMPRESSION. WILLIAM T. PEYTON and HAROLD O. PETERSON, Radiology **38**:131 (Feb.) 1942.

Basilar impression, platybasia and basilar invagination are terms used to designate a deformity of the bony structures about the foramen magnum. The cause has been variously ascribed to hydrocephalus, trauma, rickets, Paget's disease and congenital anomaly, with the majority of the evidence in favor of the last. The condition is said to be more common among Eskimos. Of a total of 26 cases collected from the literature and an additional 3 cases reported by the authors, males were affected in 17 and females in 11; in 1 case the sex was not given. The age at the time of examination varied from 17 to 70 years, the average being 34 years.

Many types of anomalous development occur about the base of the occipital bone and the upper cervical portion of the spine, and of these basilar impression is one of the most extensive. The other anomalies, such as defects of the posterior arch of the atlas, fusion or absence of the cervical vertebrae, assimilation of the atlas and manifestations of an occipital vertebra, may occur alone or as part of the features of basilar impression. All reports of cases of basilar impression in which the specimen has been dissected show that assimilation of the atlas is a

constant part of the condition. This suggests that it represents an extreme grade of a group of anomalies which may occur in this region and that they are all more or less related.

Basilar impression may be present without symptoms, but when symptoms are present they develop in adolescence or late in life. They are slowly progressive, and the condition is frequently fatal. The symptoms are so variable that a diagnosis can rarely be made in life without roentgenographic verification. The clinical manifestations may be divided into two categories: the skeletal and the neurologic. The skeletal signs consist of a short neck, with the head shifted downward between the shoulders and tilted backward, and restricted movements of the head and on the neck. The neurologic signs consist of irritation and paralysis of the cervical nerves and tracts of the spinal cord, due to compression at or near the foramen magnum; irritation or paralysis of the cranial nerves in the posterior fosa; compression of the medulla by the odontoid process; cerebellar disturbances, due to compression of the cerebellum in the shallow posterior fossa and, finally, increase in intracranial pressure.

Since basilar impression consists of anomalies of the occipital bone and upper cervical portion of the spine, it is best recognized by roentgenographic examination; a lateral view of the cervical portion of the spine, including the base of the skull, is sufficient for diagnosis. The authors believe that in all cases there is some degree of assimilation of the atlas, with fusion of the posterior arch with the occipital bone apparent in the lateral view. Chamberlain advocates drawing a line from the posterior edge of the hard palate to the posterior lip of the foramen magnum. If the odontoid process projects above this line basilar impression may be suspected. The authors agree with the correctness of this observation but find it hard at times to identify the structures in question. Changes in the basilar angle are inconstant, and alterations in the medial part of the petrous pyramids are often not present or are inconspicuous. Decrease in size and distortion of the foramen magnum are constantly seen, but may be extremely hard to demonstrate roentgenographically, owing to inability to place the patient in a position to demonstrate this because of his short and relatively immobile neck. Laminagraphy may help.

In 23 cases it was possible to determine the age at onset of symptoms, the average being 29 years. Neurologic symptoms were present in 25 cases, causing death in 10, and were absent in 4. Operation was performed in 8 cases, the operation of choice being suboccipital craniotomy and laminectomy of the upper cervical vertebrae. Cases in which operation has been performed are too few to permit of conclusions, but if it is found that such a procedure will prevent the progression of symptoms, even if there is not always restoration of function, the concept of basilar impression as a fatal disease will need to be revised.

KENNEDY, Philadelphia.

CALCIFICATION AND OSSIFICATION OF VERTEBRAL LIGAMENTS (SPONDYLITIS OSSIFICANS LIGAMENTOSA). ALBERT OPPENHEIMER, Radiology **38**:160 (Feb.) 1942.

Calcification and ossification of the vertebral ligaments are common phenomena and have not yet been distinguished clearly. Leri observed that these changes occur whenever the ligaments are subjected to strain, are torn or are involved in lesions of the vertebral bones or joints. He expressed the belief that they were evidences of healing and that the process was an effort to strengthen the weakened vertebral column. Beadle and Schmorl independently came to similar conclusions. Simmonds stated the belief that calcification and ossification may occur spontaneously as a primary syndesmosis. Cases of calcification and ossification of undetermined origin in the posterior longitudinal and interspinal ligaments and in the ligamenta flava have also been recorded.

Clinically, it is believed that the phenomena are associated with diminution or absence of motility in the region involved, such as the vertebral rigidity seen in

rhizomelic spondylosis. It was shown by Frankel, however, that this condition may not be accompanied by ossification of the ligaments and that it is produced by or associated with ankylosing inflammation of the apophysial joints. Pain low in the back has been attributed to such changes, but all authorities agree that the lesions may be present without any clinical manifestations.

The present study by Oppenheimer is concerned chiefly with the following questions: 1. Under what conditions do the vertebral ligaments calcify and ossify? 2. How are the changes in the ligaments related to lesions of the vertebral bodies, the intervertebral disks and the apophysial joints? 3. Do calcifications and ossifications of the vertebral ligaments produce stiffness of the back, pain and radicular neuritis?

Two hundred and eighty-two persons between the ages of 14 and 84 years with definite calcification and ossification of the vertebral ligaments were studied clinically and roentgenographically, many of them several times and at various intervals. Vertebral motility was tested in every case.

The longitudinal ligaments are often calcified or ossified in the presence of infection of the vertebrae, such as tuberculosis, typhoid, chronic staphylococcic osteitis, syphilis and Malta fever. Trauma may also produce the condition, and less frequently tumor metastasis. It is associated with juvenile or senile kyphosis and is most pronounced at the vertex of the concavity. It always begins here, usually remains confined to this site and may be followed by bony union of the ventral parts of the vertebrae. The process of calcification or ossification may take from three months to several years, the longer the reaction the greater the time required for the ossification, suggesting that the process is one of healing.

Oppenheimer disagrees with the commonly accepted view that the formation of osteophytes in cases of thinning of the disks is due to the tension and strain on the ligamentous structures in the region involved, since in thinning of the disks the vertebrae are brought closer together and there is obviously less strain on the ligaments. This is also demonstrated by the frequent observation that the formation of osteophytes in cases of scoliosis is more frequent on the side on which there is less strain on the ligaments, namely, on the concave side. He believes that the thinning of the disks subjects the vertebrae to repeated small traumas, and perhaps to minute fractures, and that the vertebral bone responds by a reaction which corresponds to the callus formation of other bones. Thus, the ligaments tend to limit the production of osteophytes, and it may be concluded that they play no significant part in the coexistence of osteophytes and thinning of the disks.

Examination of 50 patients with Marie-Strümpell disease showed that there was ossification of the ligamenta flava in 22 cases, of the interspinous ligaments in 12 cases and of the longitudinal ligaments in 25 cases. This ossification did not take place until at least fourteen months after the onset of symptoms. This was also true in the cases of localized apophysial arthritis, in about one-half of which the longitudinal ligaments were observed to be ossified.

The author found that calcification and ossification of the ligaments were present in a number of patients, usually those of advanced age in whom no other vertebral lesions were present. The process was most prominent in areas where the least vertebral mobility occurred and was absent in the cervical region, where the mobility of the spine was greatest. The observations seem to indicate that two factors influence the calcification and ossification of ligaments: (1) disuse of the ligament and (2) rarefaction of vertebral bone.

Vertebral mobility does not appear to be affected by the calcification and ossification of ligaments unless there is associated disease of the vertebral bodies or of the apophysial joints. Complete rigidity of the spine was observed to occur in cases of Marie-Strümpell disease without any calcification of the ligamentous structures. Frequently there is calcification in the ligaments when there has been diminished mobility for some time; hence this condition may be the result rather than the cause of diminished vertebral mobility.

It is not always possible to determine whether the pain of which the patient complains is due to the calcification of the ligaments or to the lesions of the

vertebrae which are also present. In the author's cases in which no associated lesion was present all the 16 patients were asymptomatic. He concludes, therefore, that these phenomena do not of themselves cause pain. They may compress nerve roots and cause radiculitis, but other causes should be carefully sought for before attributing the trouble to the calcification and ossification of the ligaments.

The author concludes that calcification and ossification of the vertebral ligaments is neither a clinical nor a pathologic entity; it should be considered not as an independent lesion but as a secondary reaction. Its presence often indicates a coexisting lesion of vertebral bones or joints. KENNEDY, Philadelphia.

SPONDYLITIS ADOLESCENS: STRÜMPELL-MARIE DISEASE. HARRY C. BLAIR, Surg., Gynec. & Obst. **74**:663 (March) 1942.

Synonyms for this disease are Strümpell-Marie disease, Bechterew's disease, ankylosing spondylitis, *spondylose rhizomelique* and spondylitis ankylopoietica. The clinical course is long, starting early in life with pain in the lower part of the back. This may begin as early as the age of 12 years, and ankylosis may not take place until the patient is 25 years old or more. Roentgenograms show advanced changes in the sacroiliac joint. The erythrocyte sedimentation rate is increased in proportion to the extent of involvement. This does not necessarily indicate that the cause is focal infection, since the disease occurs in cases in which there is no evidence of focal infection or in which all sources of infection have been removed. A metabolic disturbance is apparently not the cause.

Roentgenographic examination reveals widening and irregular fuzziness of the sacroiliac joints. Areas of localized absorption of bone occur nearby, or "spotty" atrophy of the adjacent portion of the sacrum is present. The cartilage is absorbed, and ankylosis of the bone takes place. The supporting ligaments become calcified, but the calcification does not spread. Roentgen therapy brings about some beneficial results. In the author's case the improvement was consistent over a period of four years. The total amount of radiation was 1,000 r, divided into sixteen doses, given twice a week, and 1,000 r distributed over a large body area.

It is possible that the roentgen rays had their action on the mast cells, since it has been demonstrated experimentally that such rays affect the sulfuric acid excretion of these cells and chondroitin sulfuric acid is found in the cartilage, tendons, ligaments and aorta. It is the author's conclusion (1) that the pathologic change in spondylitis adolescens is caused by absorption of cartilage, (2) that roentgen therapy benefits the disease by liberating sulfur within the body and (3) that in spondylitis adolescens chondroitin sulfuric acid is absorbed from the cartilage, ligaments and bone around the sacroiliac joints and spine and that this occurs because of a deficiency of sulfur or of mucoitin or chondroitin sulfuric acid elsewhere in the body. GOTTEN, Memphis, Tenn.

CONTRAST MEDIA IN CYSTS AND ABSCESSES OF THE CEREBRAL HEMISPHERE. EDGAR A. KAHN, Surg., Gynec. & Obst. **74**:983 (May) 1942.

Air and iodized poppyseed oil have been used for contrast mediums in identification of cerebral cysts and abscesses, but each has its disadvantages. A colloidal suspension of thorium dioxide has advantages over both of them. Its use in 3 reported cases of tumor allowed the surgeon to make small localized openings, thus decreasing the hazards of operation. Further localization and drainage in 3 other cases of cerebral abscess were greatly aided by injection of colloidal thorium dioxide in the original abscess cavity in which secondary drainage was necessary. GOTTEN, Memphis, Tenn.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY

ABRAHAM A. BRILL, M.D., *President, in the Chair*

Regular Meeting, Feb. 3, 1942

Physical, Psychiatric and Psychometric Studies on Postencephalitic Parkinsonism. DR. DONALD SHASKAN and (by invitation) DR. HELEN YARNELL and MISS KAREN ALPER.

Von Economo recognized the close psychosomatic relation in postencephalitic parkinsonism, but Jelliffe developed the thesis that patients with this disorder are menaced by a real and a neurotic threat. The present study was made on 27 patients in regular attendance at the neurology clinic of Bellevue Hospital. Large doses of a single tropane alkaloid were effective in decreasing the tremor of these patients and in improving their locomotion. These doses were well tolerated.

Psychologic factors are prominent in this disease and cannot be neglected in evaluating any medication. Unusually satisfactory adjustment to the disease was common to the patients in this study. They appeared to have made a satisfactory personality adjustment throughout their illness. All showed reduction of intellectual efficiency.

DISCUSSION

DR. BERNHARD DATTNER (by invitation): My experience with lethargic encephalitis dates back to 1919, when I was associated with von Economo in his earliest therapeutic endeavors. In 1921 I reported the effects of various forms of treatment of the acute and the early chronic stages of this disease, in which I stressed the benefits of an iodide solution and injections of typhoid vaccine (*Wien. klin. Wchnschr.* **34**:351, 1921). At that time the results were impressive. The rigidity disappeared, and patients who were unable to walk became mobile again, and could even run upstairs and down. It is significant, however, that this treatment has been abandoned, probably for the reason that its effect was not real. Perhaps some of the patients would have improved without any treatment, and others may have derived only a psychologic benefit.

There have been many similar therapeutic illusions in later years. In 1936, when I was the Viennese representative to Panegrossi's encephalitis clinic in Rome—one of the many foreign physicians invited by the Queen of Italy—I was at first reluctant to accept at their face value the excellent results of the so-called Bulgarian cure which were demonstrated to me. I then introduced the method in Vienna, and initially my colleagues and I apparently had more success with this treatment than with the previous simple belladonna or scopolamine therapy, which still must be considered the best available method when large doses can be administered. Gradually, however, the psychologic effect of this new therapy wore off, and we were faced with the old problem. One should, therefore, be cautious in accepting too readily therapeutic suggestions concerning this disease.

The psychosomatic relationship brought out in this paper is striking. But I do not believe that the authors are misled into thinking that the somatic and the psychologic therapeutic approach to this disease are of equal value. Schilder and others, for example, tried to influence postencephalitic tic—which is a borderline phenomenon—with hypnosis and hypnosis fortified with barbiturates and failed entirely. But I have seen the compulsive phenomena and obsessive ideas associated with oculogyric crises halted by barbiturates when they induced sleep.

The psychiatric and psychometric analyses of the authors give a new and ingenious approach to the often neglected personality of these apparently

emotionally rigid patients, and it is this contribution which was most satisfactory to me.

DR. HAROLD G. WOLFF: May I ask whether the peculiarities of personality which have been described are in any way specific? Are they observed only in this syndrome, or are they the functional defects that may be noted in any number of persons who are chronically ill?

DR. DONALD SHASKAN: I believe, and I think my co-authors will agree, that patients with this disease seem to act differently from those with other types of so-called organic disease. They appear to have some special problem. We are not prepared to say whether the psychologic or the neurologic problem is foremost.

MISS KAREN ALPER (by invitation): I should like to say a few words with reference to the findings in the personality tests. These patients have more nearly normal personalities than most of the psychopathologic group that come to the attention of our psychiatric service. They differ from normal persons in their response to personality tests of the projective type, such as the Rorschach test, in the amount of drive and the level of enterprise that they manifest and in the degree of anxiety and awareness of body disability. In the main, the responses of these patients to the Rorschach ink blots are undifferentiated and oversimplified, almost like those of an intellectually impaired subject. They, however, do not show the characteristic impotence, delayed reaction time and sense of frustration that are seen in patients with truly "organic" disease. This type of oversimplified response has a different significance with our patients than with those suffering from intellectual disability per se. It rises out of the low level of achievement which has been fixed by their lives of limited activity and total dependence rather than out of inability to cope with the situation with more intellectual enterprise. Judging from the test reactions and personality data of our patients, it is clear that they are not aware of the inadequate way in which they are meeting the test situation—that a casual response, such as "this is a tree" or "this is a butterfly," is not meeting the situation. Nothing much is expected of them in their environment. People make them feel that they are meeting a situation adequately by responding "yes" or "no" to questions about their physical needs and their restricted routine. They do not bother to accept new challenges. The situations offered them in the test situation, especially in the Rorschach examination, calls for more enterprise and activity than they have been asked to exert since the onset of their disability. It is not surprising, therefore, that these methods of probing should stir up personality reactions and patterns that are not superficially apparent. The dream material that was obtained from our patients by Dr. Yarnell stirs up anxiety that is not at all manifest in clinical interviews.

Our patients gave a great many whole responses to the Rorschach ink blots, a reaction which is, in terms of personality values, usually regarded as ambitiousness. In this instance, however, the whole responses had a different meaning. They were casual and poorly differentiated; they were not of the constructive or combinatory type but were an oversimplification of the situation presented by the Rorschach plate. Instead of ambitiousness, they expressed a marked lowering of standards—an easy way out of a situation.

In common with the records of neurotic persons with some type of body disability, our patients expressed considerable anxiety and sense of body disability in their Rorschach reactions. They differed, however, from neurotic reaction types almost as much as they did from the normal. In the records of our patients we were struck by the absence of repression or compensation mechanisms, such as dominate the personality reactions of a neurotic person with body inferiority who must still make an active adjustment in the community. None of the characteristic evasions were seen, none of the human edge details, the escape to white spaces (indicating rebellion or hostility), and only in 1 case was there a flight to fantasy. There appeared to be no active struggle with impulses and no mutilation of human figures as an expression of hostility. Human content was much

freer and more wholesome in type than it is in the neurotic person suffering from body inferiority. This difference corresponds to the difference in demands that the community makes on the neurotic person and the patient with parkinsonism. The neurotic person is required to sustain some degree of participation and adjustment despite his feelings of disability and his fears, while the community makes no demands on such obviously disabled persons as victims of parkinsonism. The neurotic person, therefore, has to acquire repressions, escapes and compensations, which are not necessary in the personality equipment of the patient with parkinsonism. The patient with parkinsonism is spared the normal wear and tear of frustration to which most people are exposed.

DR. HAROLD G. WOLFF: May I ask whether patients with another type of motility disorder which incapacitates them, such as progressive muscular dystrophy, show the same kind of reaction?

MISS KAREN ALPER: The only motor group that I have seen is the one with parkinsonism. I have done some personality studies on a group of patients suffering from sensory handicaps. I have seen only individual cases of muscular dystrophy and have not studied them systematically. Dr. Booth, who, unfortunately, is not here this evening, has made interesting comparisons of the personality types of patients with Parkinson's disease and those with hypertension, and he could say more about it. From my experience with disabled persons, I should expect a reflection of the body disability and reaction patterns in basic personality tests, such as the Rorschach test and drawings. The exact type of reaction pattern depends on how much independent adjustment in the community is expected of the patient.

DR. A. A. BRILL: It seems to me that it makes no difference whether the psychic factors enumerated by Dr. Shaskan are specific to the condition he described. What I like is Dr. Shaskan's attempt to evaluate the psychic factors. It is a fact that hitherto whenever anything was presented as "functional," one was always asked, "What about the organic part?" Neurologists never thought that they had to consider the psychic factors in their papers. However, like Dr. Wolff, I feel that as yet one cannot properly differentiate the psychic factors in the various organic diseases, but those who actually test these factors already seem to perceive something which may become more definite in the future. There is no reason that there should not be definite personality reactions to definite physical diseases. I have no doubt that patients with multiple sclerosis have a different type of personality and that their psychic reactions to the disease therefore differ, but I am glad that Dr. Shaskan examined the patients from all angles. That in itself spells progress.

DR. DONALD SHASKAN: Our point of view in relation to these patients was neurologic, and I was much interested in knowing why they responded to drugs so differently. That was my reason for starting this study. I hope that investigators in the future in describing the results of treatment of this disease will be very cautious. Patients with this disease react largely to psychologic effects. I want to point out again that all those studied showed a decrease in intellectual efficiency—a lowering of intelligence. How much that has to do with the good effects of treatment with new drugs must be considered.

Myatonic and Myotonic Reactions, as Recognized Today. DR. LEWIS I. SHARP JR. (by invitation) and DR. F. A. QUADFASEL, Brooklyn (by invitation).

A case of myatonia (Oppenheim's disease) is presented. The electrical examination with faradic and galvanic currents (both measured in milliamperes by the use of a specially constructed machine) revealed a variable decrease of excitability to electrical stimulation of muscle and nerve, corresponding to the degree of dysfunction. These changes are believed to be characteristic of myatonia. Our observations agree with those of Oppenheim and others. The myatonic formula of Collier and Wilson could not be confirmed.

The typical electrical reactions in 7 cases of myotonia (Thomsen's disease) and myotonia atrophica to stimulation with faradic and galvanic currents are demonstrated by motion picture and summarized in the accompanying table. (Motion picture was shown.)

To obtain these uniform results, one must take into account the following factors: 1. The difference in response to faradic and to galvanic current. With faradic current it is necessary to state the frequency and ratio of the closing and the opening time of one period; with galvanic current the duration of the stimulus is of importance. 2. The difference in the effect of varied strengths of current. 3. The difference in the response from the nerve and from the muscle. 4. The difference in response according to the site of stimulation of the muscle (motor point or distal to it). This reflects the development of knowledge of the electrical reaction in cases of myotonia from 1876 (Seeligmüller) to the present.

Data on Electrical Stimulation in Cases of Myotonia

		Muscle	
	Nerve	Motor Point	Distal to Motor Point
Faradic (interrupted)			
Minimal strength	Unsustained tetanus (normal); tightening for 1 to 2 sec. afterward	Unsustained tetanus (normal); tightening for 1 to 2 sec. afterward	No response
Medium strength	Tetanic contraction; persistence of contraction, on repetition gradually decreasing and disappearing (to normal)	Tetanic contraction; persistence of contraction, on repetition gradually becoming normal; sometimes groove formation	No response
Strong			Localized tetanic contraction
Galvanic (constant)			
Minimal strength	Single swift contraction; no persistence of contraction	Single swift contraction; no persistence	Slow or continuous contraction as long as current is allowed to flow
Medium strength		Single swift contraction and slow contraction, or continuous contraction, sometimes gradually increasing; no persistence	
Strong	Tetanic contraction; persistence of contraction	Tetanic contraction and persistence	Continuous contraction; slow subsidence after opening of current
Accrescence of current	Possible without reaction beyond threshold strength	Possible without reaction beyond threshold strength	Not possible without contraction at threshold strength
Chronaxia	Normal	Normal	Increased

The characteristic myotonic reaction as it is recognized today is the persistence of the contraction on faradic stimulation of nerve and muscle and the double reaction of the muscle on galvanic stimulation, that is, the quick reaction from the nerve or the motor point and the slow, wormlike or the continuous contraction from a point distal to the motor point.

The motion picture shows also the dual contraction on isolated voluntary innervation of an individual muscle (biceps) and the disappearance of the myotonic reaction after injection of quinine dihydrochloride (0.65 Gm.) intravenously.

The electrical myotonic reaction suggests that the localization of the pathologic process of myotonia is in the muscle proper. However, one must not forget that a pathologic muscle, when acting as part of an integral, behaves differently, as Denny-Brown has recently pointed out, than an isolated muscle preparation or a peripherally induced response. The role of compensatory mechanisms in the normal function of a myotonic limb cannot be determined by this electrical examination.

In papers to be published we shall discuss the history of the electrical reactions of myatonia and myotonia and more specialized aspects of the problem.

DISCUSSION

DR. E. D. FRIEDMAN: The film speaks for itself. I should like to make one comment with regard to the reaction in myatonia. Oppenheim expressed the opinion that children with this disorder could stand high degrees of stimulation with faradic current without evidence of pain. In one or two instances I have not been able to convince myself of that fact, and it is interesting to hear from Dr. Sharp that he also found that Oppenheim's statement did not hold.

The film on myotonia is a beautiful example of careful work done under controlled conditions with a special apparatus which brings out all the details of muscular contraction. It is interesting to observe that the Jolly reaction, which was deemed characteristic of myasthenia gravis, was present. It is known that this reaction is not characteristic of myasthenia gravis but can be found in normal persons, and now it is demonstrated in patients who present the antithesis of myasthenia gravis.

Psychoanalytic Interpretation of the Mental Symptoms of Dementia Paralytica. DR. ISADOR H. CORIAT, Boston (by invitation).

The psychoanalytic interpretation of either the organic or the so-called functional psychoses is not a speculative system of ideas but is the result of experience founded on direct observation. Psychoanalysis has been fruitful in its investigations into the deeper dynamics of the psychoses, in contradistinction to the purely statistical compilation and a more or less rigid classification of mental disorders. Mental symptoms are not due to chance but can be interpreted in somewhat the same manner that the psychoneuroses have been reconstructed. The principal psychoanalytic investigations on the psychoses have been made on schizophrenia, the relations of libido development to mental disorders and the deeper mechanisms of projection in paranoid reactions. The findings constitute an internal phenomenology of a dynamic psychiatry, which has been a great advance over the external phenomenology of the cataloguing of symptoms in general psychiatry.

The analytic interpretation of the psychic disorder of dementia paralytica received its first consideration in a monograph by Hollós and Ferenczi (Psychoanalysis and the Psychic Disorder of General Paresis, *Psychoanalyt. Rev.* **12**:88, 1925). Although the central problem of this disease is dementia, the special character of the dementia can be understood only when the various psychic levels which are affected can be explained and dynamically reconstructed. Even in the organic psychoses, as in the psychoneuroses, there are many mechanisms which can be explained psychoanalytically.

Ferenczi formulated the conception of pathoneuroses, that is, a special narcissistic neurosis which develops as a consequence of falling ill or of injury to organs, particularly those organs which are the most important to life or are highly prized by the ego. He ventures the hypothesis that at least part of the mental symptoms of dementia paralytica are manifestations of what he terms a "cerebral pathoneurosis," traced in part to libido discharge and in part to a narcissistic intensification of the libido provoked by the organic lesion. The syphilitic infection of the brain attacks the central organ of the ego function, thus producing the symptoms of this mental disorder.

The clinical histories of 3 cases of dementia paralytica, with their psychoanalytic interpretations, are given. In all these cases there was profound shattering of the sense of reality. In 1 instance there was a peculiar amnesia, a regression to an earlier stage of libido organization and wish-fulfilling fantasies to compensate for a reality situation. In another case it could be demonstrated that the forgetting or denial of the syphilitic infection was a result of the fact that a patient with dementia paralytica wishes to repress altogether not only insight into his disease but likewise its specific causation. In a third case, in which the disease was associated with tales and extravagant delusions of grandeur and power, it could be shown that this delusional magic was a wish fulfilment which compensated for an unbearable reality.

Dementia paralytica affects not only the integrity of the ego, but the libidinal drives of the id, producing a symptomatology closely analogous to that of dreams, all of which shows that mental symptoms and changes in cortical structure seem to be interrelated. The psychodynamic viewpoint tends to equate an organic disease of the brain with the symptoms of a severe psychosis—what may be termed a castration of the entire mental apparatus. The ego loses its reality-testing relation to the external world and so retreats to the dream world of exaggerated and distorted fantasy; the superego is so weakened and shattered that it cannot control the libidinal drives of the id, so that the libido of the patient with dementia paralytica regresses to an earlier level.

The ego is a function of the cerebral cortex, and consequently the cortical devastation of dementia paralytica affects the ego directly. The ego is also the direct instrument of deeper instinctual levels, and so the inroads of the organic process produce various symptoms of libidinal regression.

DISCUSSION

DR. GERALD R. JAMEISON (by invitation): Dr. Coriat's paper is appropriate today, particularly as the total reaction of the personality to disease, in the emphasis on psychosomatic medicine, is again being stressed.

There is an aspect of dementia paralytica that is not entirely a hopeless one. The organic condition is treated with shock therapy, malaria, and so on, but there is a residual reaction which is the personality. Does the actual infection produce these mood reactions and these various trends? It is evident that the infection in itself does not cause these reactions, that whatever is released in terms of symptoms is the same thing that is released in the functional psychoses, in which no physical etiologic factor is concerned; in other words, the mood, the trend, the progressions and regressions are related to the personality and are perhaps the precipitating factors. In dementia paralytica, and in any of the organic conditions, there are acute precipitating factors, as there are in the functional reactions.

DR. C. P. OBERNDORF: I should like to comment on two questions which Dr. Coriat raised. The first is whether these mechanisms which he described so graphically are specific to dementia paralytica, or whether one does not find rather similar mechanisms in other wasting diseases in which the organic structure involved is not primarily in the brain but in other organs, such as cancer or tuberculosis. To attribute the selected psychoanalytic mechanisms which were observed in patients with dementia paralytica to a spastic destruction of the brain cells, rather than to general wasting away of all ego functions, is open to discussion, and I hope Dr. Coriat will touch on this.

The second point is whether if the withdrawal from reality and regression associated with dementia paralytica is due to organic changes, Dr. Coriat would also say that the converse is true, namely, that when such symptoms are particularly pronounced, as in schizophrenia, some organic change is present in the brain.

DR. WALTER S. BÖRNSTEIN (by invitation): In his first case, Dr. Coriat stated that the patient had voracious hunger, and I understood him to say that this meant a regression to the pregenital oral phase. Several authors, from von Bechterew to Fulton, have shown that certain lesions of the frontal lobe, for example, those of dementia paralytica—produce voracious hunger. I should like to ask Dr. Coriat whether such a lesion might not account for the voracious hunger in his case.

DR. A. A. BRILL: My psychoanalytic practice started under Bleuler, and the first literature on the subject which I read were two of his papers on freudian mechanisms in the symptomatology of the psychoses (*Psychiat.-neurol. Wchnschr.* **8**:316, 323 and 338, 1906-1907), in which he stated that dementia paralytica and other organic diseases display freudian mechanisms. There is no reason that any damage to the personality should not be reflected in the mind, and the best way of studying it is by psychoanalysis. As far as I recall, no one has said

anything about the psychoanalytic mechanisms of dementia paralytica since Hollós and Ferenczi published their monograph. There is no doubt that organic deterioration produces regression to the infantile level. I recall a case of this kind. When I saw the extremely deteriorated, senile patient, he was sitting like a child with his thumb in his mouth. Formerly, he continually held his pipe in his mouth. The family physician, thinking that tobacco was not good for his heart, had taken it away from him, and he immediately began to suck his thumb. I suggested that his pipe be returned to him, and he then abandoned thumb sucking. Here was a definite regression to childhood, but it was only one of others. It is known that thumb sucking and smoking represent one and the same thing; the latter represents a higher level of the same oral gratification.

Voraciousness may be due to a lesion of the frontal lobe, which may occur in dementia paralytica, but I have observed the case of a woman who showed pronounced voraciousness after her husband's death. In her attacks she consumed enormous quantities of food. There was nothing organic in her condition, which I cured by psychotherapy. Such a symptom may be due to an organic condition, but I have never seen an instance. I reported a similar case (Alcohol and the Individual, *New York M. J.* **109**:928 [May 31] 1919) in a young woman whom I treated by analysis, and she has been well since. There was really nothing organic in her case.

Dr. Isador H. Coriat, Boston: I noticed in the first paper of the evening, as well as in my own, that psychosomatic medicine was emphasized; I think this psychosomatic approach is attracting its present attention because it offers a borderland between analytic psychiatry and internal medicine. I agree that both psychoneuroses and organic psychoses may have similar reactive mechanisms to adult objective reality situations. There is nothing particularly original in the psychodynamic viewpoint of my paper, but I was aware that the analytic interpretation of dementia paralytica, so far as I could gather from the literature, had been practically neglected since the publication of the monograph by Hollós and Ferenczi. Similar mechanisms may occur in all organic diseases of the brain. So far as is known, there are no organic changes in schizophrenia; yet the schizophrenic patient regresses. The exact dynamics of this regression are unknown.

As for voracious hunger in cases of lesions of the frontal lobe, I am willing to concede the observations of the physiologists.

In reading the paper, I mentioned 2 men prominent in literature who suffered from dementia paralytica—de Maupassant and Nietzsche. The material on both these writers is abundant, and I found, on going over some of it recently, that both men had had frustrations in their life situation, particularly Nietzsche, whose first symptom following his narcissistic wounding consisted of delusions of grandeur.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

George H. Hyslop, M.D., *Chairman of the Section of Neurology and Psychiatry, Presiding*

Joint Meeting, March 10, 1942.

Paraphenylendiamine Poisoning and the Central Nervous System. Dr. Charles Davison.

The prevalent use by women of coal tar products as hair dyes, sold in the market under various trade names, is well known. "Ursol," a paraphenylandiamine coal tar chemical, is a popular preparation. When such a dye is used excessively, vertigo, gastritis, diplopia, asthenia and exfoliative dermatitis may result. Although neurologic complications, such as dizziness, nystagmus and tin-

nitus have been recorded, histopathologic reports of involvement of the central nervous system were not found in the literature.

REPORT OF A CASE

L. M., a woman aged 51, was admitted to the Montefiore Hospital on Dec. 22, 1939 with a history that for about a year and a half she had been using "ursol" in dyeing her hair. In December 1938 she experienced pain in the knees. In June 1939 she noticed a yellowish discoloration of the skin of the entire body and of the finger nails. In August 1939 she complained of dyspnea on exertion, occasional palpitation and loss of about 30 pounds (13.6 Kg.) in weight. During this interval there was a low grade fever. In the early part of September 1939 tender blisters appeared over the tongue; these slowly subsided. At this time she suffered from abdominal pain, severe anorexia and weakness.

Physical Examination.—The discoloration of the skin of the body and of the nails matched the color of the dyed hair. The dorsum of the tongue was smooth. The heart was slightly enlarged to the left and the second aortic sound was greater than the second pulmonic. There was some evidence of auricular fibrillation. The blood pressure was 110 systolic and 70 diastolic. The liver was 4 fingerbreadths and the spleen 3 fingerbreadths below the costal margin. Motion of the interphalangeal joints was decreased.

Neurologic Examination.—There were deep muscle tenderness over both calves; slightly exaggerated reflexes, especially in the lower extremities; left ankle clonus; absence of abdominal reflexes, and a questionable Babinski sign bilaterally. No evidence of sensory change was apparent. There was suggestive facial paralysis of supranuclear type.

Laboratory Data.—The urine contained albumin, 2 white cells per cubic millimeter and granular and hyaline casts. Examination of the blood disclosed 72 per cent hemoglobin, 3,600,000 red cells and 5,750 white cells, with 38 per cent polymorphonuclear leukocytes, 16 per cent metamyelocytes, 2 per cent myeloblasts, 27 per cent lymphocytes, 4 per cent mononuclears, 2 per cent eosinophils and 1 per cent basophils. The blood smear showed evidence of anisocytosis, macrocytosis, poikilocytosis and polychromatophilia.

Roentgen examination of the skeletal system revealed hypertrophic changes in the spine, hip joints, sacroiliac bones and bones of the lower extremities and hands.

Course.—During her stay in the hospital the patient complained repeatedly of severe asthenia, anorexia and epigastric pain and appeared very drowsy. She had a low grade fever, the temperature being between 99 and 100 F. and rising nightly to 102 F. She received all forms of vitamin therapy, which led to disappearance of the glossitis. The neurologic picture remained unchanged. The aforementioned symptoms were most severe in February, when she also displayed increased drowsiness. During this period the knee and ankle jerks were unobtainable, and there were a definite left ankle clonus and plantar responses. She received several transfusions, but gradually grew worse and died on March 9, 1940.

The results of autopsy are reported (lantern slide demonstration).

DISCUSSION

DR. MOSES KESCHNER: Ordinarily, cases of the type just presented by Dr. Davison do not come under the observation of neurologists until the onset of serious manifestations indicative of involvement of the central or the peripheral nervous system. The neurologist, therefore, rarely has an opportunity to study such cases early in the evolution of the clinical picture. It is for this reason that I regard Dr. Davison's presentation as a valuable contribution to a branch of medicine which hitherto has attracted the attention mainly of industrial chemists, dermatologists, allergists and internists.

The neural complications observed in cases of poisoning from the use of cosmetics the chief ingredients of which are benzene ring derivatives, as well as from the use of these products in the fur, feather and hose-dyeing industries, have been mentioned by Dr. Davison, and there is no necessity to comment further on this phase of the problem. Dr. Victor Rosen and I reported a case of intraocular optic neuritis with papilledema and retinal hemorrhages following one application of a hair dye containing paraphenylendiamine, which is known commercially as "Glo-Rnz" (Keschner, M., and Rosen, V.: Optic Neuritis Caused by a Coal Tar Hair Dye, *Arch. Ophth.* **25**:1020-1024 [June] 1941). Dr. Davison referred to this case in his presentation.

It may be of interest, however, to call attention to the histologic changes in the nervous system in Dr. Davison's case. These seem to resemble closely the changes observed in the brains of patients with the Wilson pseudosclerosis–hepatolenticular degeneration group of diseases; they also resemble in some respects the changes in the brains of animals following ligation of the common bile duct (Crandall, L. A., and Weil, A.: Pathology of Central Nervous System in Diseases of the Liver, ARCH. NEUROL. & PSYCHIAT. **29**:1066 [May] 1933). The only striking difference in the histologic picture is that in cases of the Wilson disease group the putamen is usually more affected than the pallidum whereas in Dr. Davison's case the pallidum was more affected. The histologic changes in the brain in the case presented tonight, when taken into consideration with the presence of the hepatosplenomegaly, raise the question whether in some of the cases in the Wilson disease group the changes in the brain and liver, generally assumed to be predetermined genetically, may not have been due to an exogenous factor. Such a factor may be chronic poisoning from the ingestion of prepared foods which, in order to increase their appetizing quality, have been colored with synthetic products of the benzene ring derivatives (aniline). Or one may consider the role of prolonged exposure to similar toxic compounds in the course of occupations in which the amazing growth of the aniline dye industry plays a significant part.

Cases of the type presented by Dr. Davison may well be a starting point for research on the etiology of the aforementioned syndromes, which are regarded by some observers as belonging to the heredofamilial group of diseases and by others to be due to some unknown endogenous toxin. I have in mind 2 patients whom I had under observation. The clinical diagnosis was Wilson's disease, but the patients, instead of dying, actually improved and are still living, more than a decade since the onset of the illness. Of course, no one can tell what histologic examination of the brains of these patients might show. On clinical grounds, however, such cases raise the question whether the disease may not be due to an exogenous factor rather than to an endogenous toxin of a sort that Wilson must have had in mind when he originally described his cases.

DR. RICHARD BRICKNER: Is there any way of confirming the diagnosis, such as chemical tests, during life, or is the diagnosis made solely from the history of the use of these materials?

DR. HENRY A. RILEY: What is the status of this material under the Pure Food and Drug Act?

DR. CHARLES DAVISON: In answer to Dr. Brickner, the discoloration of the skin usually matches the color of the dye. Careful questioning of the patient will also help.

As to Dr. Riley's question: The following note appeared on the label of the product Glo-Rnz, as required for all coal tar hair dyes by the Federal Food, Drug and Cosmetic Act: "This product contains ingredients which may cause skin irritation on certain individuals, and a preliminary test according to the accompanying directions should be made. This product must not be used for dyeing the eyelashes or eyebrows, to do so may cause blindness."

Development of Neurosurgery in New York City During the Past Twenty-Five Years, with Comment on Advances Due to Experiences in the First World War. DR. CHARLES A. ELSBERG.

In New York, and in the United States, neurosurgery began to be recognized as a special field only a little more than twenty-five years ago. Before that period relatively few operations were performed on the central nervous system, and these by general surgeons. Some of the earliest operations for tumor of the brain performed in New York city were done by Dr. Charles McBurney, at the Roosevelt Hospital, by Dr. Arpad G. Gerster, at Mount Sinai Hospital, and by Dr. Andrew J. McCosh, at the Presbyterian Hospital. In 1892, Hartley described the operation for the intracranial exposure of the gasserian ganglion which was for many years known as the Hartley-Krause operation. A neurologist of this city, Dr. M. Allen Starr, published in 1893 the first book on brain surgery in the United States. The surgical advice given in that book, only about fifty years ago, sounds quaint today: "It is an absolute requisite of success in cerebral operations that every detail of aseptic surgery shall be carried out to perfection. It is useless to make elaborate preparations, to sterilize instruments and to apply antiseptic solutions to the hands, if in the midst of the operation the surgeon stops for a moment to adjust his septic eyeglass, or to blow his nose on a septic handkerchief without subsequently washing his hands again."

During the past twenty-five years neurosurgeons in New York city have made many contributions to neurology and to the special branch of neurosurgery. They made and published many investigations on the symptoms, diagnosis and treatment of tumors and other diseases of the spinal cord. They standardized the technics of laminectomy and hemilaminectomy and worked out the procedure for the exposure of the anterior surface of the spinal cord. The syndromes of the so-called giant tumor of the conus and cauda equina, of varicosities of the spinal veins and of extradural cyst of the spinal cord were first described by New York neurosurgeons and their associates. In association with a roentgenologist, one of the workers in this field described the method of measuring the size of the vertebral canal on roentgenograms of the spine and showed that enlargement of the interpediculate distances occurred in association with many tumors of the spinal cord, especially the perineurial fibroblastoma, and occurred regularly with lipomas in special locations, with extradural and intradural cysts and with giant tumors of the conus and cauda equina. The same authors described the roentgenologic methods by which small benign tumors beneath the frontal lobe of the brain can be recognized.

Advances in knowledge of neurology and neurosurgery made from experiences in the first World War and their significance for the treatment of injuries of the brain, spinal cord and peripheral nerves in the present conflict are mentioned. Other contributions to neurology and neurosurgery which had been made by New York neurosurgeons and neurologists are demonstrated by lantern slides.

Because of the often rapid progression of symptoms and signs, the malignant tumor of the brain called glioblastoma multiforme was called "acute brain tumor" by authors from this city. The operative results are poor and mainly palliative. In the future, in most cases, some other method of treatment must be found—perhaps it will be serologic or roentgenologic. The tumor called medulloblastoma, which occurs so often in the midline of the posterior cranial fossa in children, cannot usually be completely removed. This type of growth is extremely radiosensitive. As good, or better, results can be obtained by conservative surgical treatment (suboccipital craniotomy with removal of only enough tumor tissue for verification) and roentgen therapy than by attempts at radical removal of the growth. With this plan of procedure, not only is the operative mortality smaller but the patients live as long and are as much relieved after roentgen therapy without removal of the growth as after attempted radical excision.

Neuropsychiatric Problems Concerned with Burn Encephalopathies of Childhood. DR. LAURETTA BENDER.

In the children's ward of the Psychiatric Division of Bellevue Hospital since 1934 several children have been seen who presented all the problems associated with chronic encephalitis, such as the typical disturbances in behavior, the specific disturbances in intellectual function and the characteristic neurologic signs. These children, however, had no history of encephalitis but, instead, had suffered from extensive burn of the body surface in early childhood, from which time their behavioral, intellectual and neurologic disturbances were dated.

Globus and Morris Bender reported a case of disseminated toxic degenerative encephalopathy secondary to an extensive burn in an 8 year old boy who lived for six months after the burn. He had a stormy clinical course, with initial shock, anuria, vomiting, infection of the wound and progressive mental signs of a regressive type.

Pruse reported the case of a 15 month old child with a severe burn who did well for a month and then had a series of convulsions with high fever, followed by multiple signs of involvement of the brain.

Roth described the case of an 8 year old child observed in the wards of Bellevue Hospital in 1940 who after a severe burn had convulsions and coma with a high fever on the twentieth day, after which she displayed aphasia and intellectual regression. The present study includes a follow-up study of this last child, who has improved progressively but is still partially aphasic, shows the impulsive behavior of the postencephalitic child and has mild neurologic signs involving the right side.

Eight other cases are reported of children with burns in early childhood who subsequently presented typical postencephalitic behavior problems, with disturbances in intellectual functioning, especially in integration of perceptual material, and neurologic signs. These cases are compared with cases studied in the children's ward and cases of other types of encephalopathies observed during the same period. They seemed to be most similar to cases in which the child had suffered from the pyogenic type of encephalitis in early childhood.

This paper will be published in full elsewhere.

DISCUSSION

DR. MORRIS B. BENDER: Verified cases of encephalopathy due to severe burns of the body are rare. Postmortem examination of the brain of a victim who died shortly after sustaining the burn usually reveals hyperemia of tissues of the central nervous system. On the other hand, if a patient survives for any length of time, such as weeks or months, pronounced encephalopathia may exist. The neuropathologic changes are usually diffuse and resemble those seen in brains of animals given injections of toxin. Clinically there may be no signs of a focal lesion in the nervous system. In the acute stage, if the systemic reaction is pronounced and the patient lives, a transient period of delirium may occur, but as a rule there are no mental symptoms until late in the course of the disease.

In the cases which Dr. Lauretta Bender reported the interval between the time when the burn occurred and the onset of the behavior problem was rather long. In fact, it was so long that one may doubt whether there was any relation between the two. There is always the question whether the child was a behavior problem to begin with and, because of this, burned himself. It is possible, however, that psychopathic behavior disorders may appear years after a secondary burn encephalopathy, as they are known to do after encephalitis of traumatic, infections or virus origin.

DR. HENRY A. RILEY: I presume there has been no opportunity to investigate the cytologic structure of the brains of these children. I am wondering whether it would be feasible to carry out brain puncture and make a microscopic examination of the material removed, as was done several years ago in the investigation of schizophrenic patients. This can be done by removing a core of cortical tissue through a small auger hole in the skull.

DR. LAURETTA BENDER: I am sure it would be possible, especially as most of these children are going eventually to state hospitals. I think it would be merely a question of the technical problems involved, and I see no reason that it should not be done.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

H. HOUSTON MERRITT, M.D., *Presiding*

Regular Meeting, March 19, 1942

Electroencephalographic Study of Two Hundred Seventy-Four Candidates for Military Service. DR. JOHN E. HARTY, MRS. ERNA L. GIBBS and DR. FREDERIC A. GIBBS.

How to prevent men with neuropsychiatric disorders from being enrolled in the armed forces is a problem which has recently received much attention. Farrell (Lectures on Military Psychiatry, delivered before the Neuropsychiatric Seminar, Metropolitan State Hospital, Waltham, Mass., 1941) gave figures indicating that about 50 per cent of all discharges for disability during military training are for neurologic and psychiatric defects. Von Storch and associates (*New England J. Med.* **224**:880-897, 1941) pointed out that a large proportion of the men discharged for neuropsychiatric disability in the first World War presented a previous history of these disorders, and Bloomberg and Hyde showed that rigorous prior elimination of men with evidence of neurologic or psychiatric disorder reduces the rate of discharge.

The present study was undertaken to determine whether in the selection of men for the armed forces the electroencephalograph is a valuable adjunct to the neuropsychiatric examination. It was believed that disorders of cortical activity might occur in a high proportion of men with certain types of neuropsychiatric disorders and that if this was so, the presence of abnormalities in the electroencephalogram might be used as objective evidence of unfitness.

MATERIAL AND METHOD

Two hundred and seventy-four candidates for military service were studied at the induction center, Fourth Recruiting District. The electrical activity of the left and right frontal, parietal and occipital areas (indifferent electrode on both ears) was recorded with a Grass 3 channel electroencephalograph. A neuropsychiatric history was obtained from each candidate, with particular emphasis on performance in school, occupational record, social history, family history and presence or absence of signs and symptoms of disorder of the central nervous system. Electroencephalograms were classified independently of the clinical record.

RESULTS

The incidence of abnormal electroencephalograms in the entire group of 274 men was 30 per cent. This is extraordinarily high. In a control group of superior subjects, consisting of medical students and the hospital staff, the incidence of abnormal records was only 15 per cent.

We believe that this is an indication of the inferiority of the sample. When men with a history of severe injury to the head or neuropsychiatric disorders were excluded, the incidence of abnormal electroencephalograms fell to 15 per cent. On general social and psychiatric grounds, also, it was obvious that this sample was below the average. Why, in the early stages of the present emergency, so unsatisfactory a sample of the population was obtained for enrolment in the army is beyond the scope of the present report. It suffices to point out that at the time this study was carried out, local draft boards were inclined to exempt stable and capable members of the community and to refuse exemption to those whom they considered undesirable. On the other hand, the unemployable and the

socially rejected often sought to join the Army as a means of escape, either by volunteering or by not seeking deferment. The incidence of psychiatric disorders and of abnormal electroencephalograms would probably have been lower at a later date. For purposes of correlating the present problem of clinical and electroencephalographic disorders, the high incidence of abnormality is an advantage, for it provides a large number of cases of extreme instability, such as are ordinarily encountered only in a large sample.

There were an 88 per cent incidence of abnormal electroencephalograms among men with psychopathic personalities (8 cases), a 60 per cent incidence among men who had a family history of epilepsy (8 cases) and a 50 per cent incidence among men with convulsions only in infancy (4 cases). There was a 60 per cent incidence of abnormal electroencephalograms among men with various functional disorders, such as enuresis, temper tantrums and sleep walking (53 cases). Among men whose history was noncontributory except for head injury with unconsciousness (61 cases), the incidence of abnormal electroencephalograms was 28 per cent, whereas among those with head injury without unconsciousness (10 cases) the incidence of abnormal electroencephalograms was 11 per cent. An 11 per cent incidence of abnormal electroencephalograms was also found among men with a noncontributory history except for that of headache. The last observation is interesting, for it suggests that in spite of the relation that is believed to exist between epilepsy and migraine, a group of men subject to headaches are from an electroencephalographic standpoint a superior group, in contrast to a group with a history of seizures in infancy or a family history of epilepsy.

Of the men with a petit mal or a psychomotor type of electroencephalogram 86 per cent (7 cases) had a history of neuropsychiatric disorder; of men with abnormally slow electroencephalograms, 82 per cent, and of men with a dominant frequency of 10½ per second, 34 per cent, had a history of neuropsychiatric disorder. Of the men accepted for military service, 28 per cent had abnormal electroencephalograms. Of the men rejected, 36 per cent had abnormal electroencephalograms. Of the men rejected for neuropsychiatric reasons, 55 per cent had abnormal electroencephalograms.

From these figures, it appears that there is a significant relation between abnormalities in the electroencephalogram and a history of neuropsychiatric disorders and that the electroencephalogram could be combined with other tests to determine fitness for military service.

DISCUSSION

Dr. Hallowell Davis: Is the term "abnormal' used synonomously with "slow frequency" and "fast frequency"? The distinction between the slow 1 and the slow 2 type was not shown in the first slides. What is the difference between them, and should they both be classified as abnormal? From my own experience at the Naval Hospital, Pensacola, Fla., in examining a group of men thoroughly screened by previous examinations, it is my impression that the electroencephalograms of naval aviation cadets follow closely the distribution of the normal group described by Dr. Harty and his collaborators.

Dr. Robert S. Schwab: In this study, some of the men had had their breakfasts, but a large number of them were fasting when their brain waves were recorded. My associates and I at the Massachusetts General Hospital have found rather strong evidence that it is important to maintain a normally high blood sugar in order to determine the fine point between normal and abnormal rhythm, and I wonder whether the authors took this into consideration. Dr. Mary A. B. Brazier, working at the Massachusetts General Hospital, has also found a rather high percentage of minor abnormal variations in a group of otherwise normal patients. I wonder whether the abnormal electroencephalogram is not being based too closely on small changes in frequencies—in other words, whether the "abnormal" does not include many variations which should be considered normal.

Dr. Leon J. Robinson, Palmer, Mass.: The question is important because epilepsy seems to be on the increase among registrants. I have been called on

to make electroencephalograms for many of the induction boards in western Massachusetts. My colleagues and I have been faced with the problem of registrants who have passed their physical examination and are not known to have any history of psychiatric disorders, but who claim they have epilepsy, perhaps not for purposes of malingering, but they do claim the disability. We have found that the true malingerers show a surprisingly high percentage of normal electroencephalograms. On the other hand, we have noted a number of wave and spike forms in several patients who claimed to have had convulsions in the past ten years but who have been scouted as not having anything wrong with them. In 1 case a man claimed that he had occasional fainting spells, but could not prove it and showed normal leads from the right frontal, motor and occipital and the left frontal and occipital areas; we were beginning to think there was nothing wrong, when we took the record from the left motor lead, which, much to our astonishment, showed slow waves. The other areas were normal.

DR. HENRY R. VIETS: It is not quite clear to me how these 274 candidates were chosen. Were they selected for this examination because of a potential psychiatric disorder? I should like, also, to ask Dr. Harty for his opinion of the possible present value of the electroencephalogram in excluding persons from military service.

DR. KNOX H. FINLEY: I have had occasion to make electroencephalograms on a few selectees and have also found some abnormal tracings, although in this smaller series the percentage was not as high as that given by the authors. They point out a high percentage of abnormal records among the psychopathic personalities. The percentage of abnormal records obtained for 50 to 75 patients at the Boston Psychopathic Hospital whose condition was diagnosed as psychopathic came nearer the normal than the percentage of such records from patients with any other type of neuropsychiatric disorder, including the psychoneuroses.

DR. D. DENNY-BROWN: It is gratifying to find the electroencephalographic paralleling the clinical impression. The crucial point is that small group, about 13 per cent, of subjects who, though not having had a previous injury to the head and not having a psychopathic personality, still have an abnormal electroencephalogram. In that group of subjects, whose status was not assessed by clinical means, is the electroencephalographic abnormality of significance or not? I suspect that Drs. Harty, Gibbs and Gibbs will say that they wish to see what happens to this group. Have these subjects any particular abnormality?

DR. JOHN HARTY: We tried to obtain a random sample of the men coming up for examination. We were working in collaboration with two draft boards; the recruiting sergeant merely checked off every sixth or seventh man and sent him in to our booth for an electroencephalogram.

As to my impression of the practical value of the electroencephalogram as a clinical or selective test, I should say it has definite value as an objective test in borderline cases in which there is doubt as to whether a man should be accepted or rejected. It should always be used, however, in conjunction with other clinical data. I believe, however, that further study is needed on large groups before the electroencephalogram can be given definite predictive value.

DR. FREDERIC GIBBS: In order to test the correlation between the electroencephalogram and the examining board's judgment of a man's fitness, the board was not informed of the electroencephalographic findings. The percentage of abnormal records among men who were rejected is therefore a true indication of the association between separate variables.

Dr. Davis asked what we consider abnormal. We use the term abnormal only to provide a coarse summary. We apply it to any record which deviates far enough from the normal, or center of our distribution curve, to be unusual. Where in our classification we draw the line between normal and abnormal depends on the age of the group being studied. For young adults we consider as abnormal

any frequency slower than 8½ or faster than 12 per second. The subdivision of the groups with the slow and the high voltage fast frequencies was made because experience proved that it was in general profitable. The slow 2 type of record is very slow, and the fast 2 type is very fast. The distinction is based not only on frequency but on amplitude, as well as on the percentage of the record occupied by the frequency in question.

Dr. Schwab has suggested that a low blood sugar level may have increased the number of abnormal records in this group. None of these men were studied before 9 a. m. They had all presumably eaten breakfast. Even if they were fasting, we should not expect to find blood sugar levels below 40 mg. per hundred cubic centimeters. It would be worth while to investigate the degree of correlation between normal variations in the blood sugar level and the type of abnormality we are studying here. We should not expect to find much correlation, however, for in normal controls we have not been able to produce abnormalities by lowering the blood sugar until the level of sugar fell below 50 mg. per hundred cubic centimeters. We have shown that in this group there was a correlation between the neuropsychiatric history and the electroencephalogram That is the point which we wish to stress. There may have been variations in the sugar level which modified the electroencephalogram; nevertheless, the correlation remains. Dr. Schwab asks whether we have not included too broad a band under the heading "abnormal." Where one should draw the line is arbitrary. It is true that for certain purposes it may be disadvantageous to include the slow 1 or the fast 1 with the more extreme categories. In the present study, however, experimentation with the data showed that the divisions used here were advantageous.

I am interested to hear that Dr. Robinson has in several instances found seizure discharges in draftees who were reported to have had seizures but who were suspected of malingering. On several occasions we have reported seizure discharges in men who presumably had had no clinical seizures but who shortly afterward began to have them. This, of course, is largely accidental, for there is no reason that a man should start having clinical seizures a week or two after seizure discharges are detected in his electroencephalogram. All we can say is that a man with seizure discharges has a vastly greater chance of having clinical epilepsy than a man with a normal record.

Dr. Finley stated that he did not find a high incidence of abnormal electroencephalograms among patients with psychopathic personalities. Our group is small, only 8 men, and it may prove to represent a highly selected type of psychopathic personality, perhaps the epileptoid, whereas Dr. Finley's may contain a high proportion of schizophrenic or manic-depressive types.

Dr. Denny-Brown points to the interesting group of men who were quite normal clinically and yet had abnormal electroencephalograms. I agree that it would be interesting to follow them, but I believe that when the entire story is in there will still be a group with abnormal electroencephalograms but normal histories. Abnormalities in the electrical activity of the cortex tend to accompany disturbances in behavior, but they do not necessarily do so. Whether persons with abnormal electroencephalograms and no clinical evidence of disorder are to be considered normal will depend on the point of view, on the functions or groups of functions under consideration, on the fineness of the tests applied and on the procedures or stresses that are used to bring out latent abnormalities. It should be remembered that in some cases the abnormality may appear as abnormal behavior only in the offspring.

Some Problems of Wartime Neurology. DR. WILDER PENFIELD, Montreal, Canada.

This paper was published in the May 1942 issue of the ARCHIVES, page 839.

PHILADELPHIA NEUROLOGICAL SOCIETY

ROBERT A. GROFF, M.D., *Presiding*

Regular Meeting, March 27, 1942

Extramedullary Tumor of the Medulla: Report of a Case. DR. PAUL SLOANE and DR. ALEXANDER SILVERSTEIN.

H. L., a white man aged 31, a news dealer, was admitted to the Mount Sinai Hospital on Sept. 14, 1939. A diagnosis of bronchopneumonia was made, and he was treated accordingly. On recovery from the respiratory infection the patient began to complain of numbness and tingling in the right arm and leg. A neurologic examination at this time revealed many diffuse signs, showing involvement of the pyramidal tracts, the posterior columns, the cerebellum and the anterior horn cells of the upper cervical portion of the cord.

The neurologic signs progressed. Atrophy and weakness of the right side of the tongue, nasal speech and some difficulty in swallowing appeared. The spinal fluid pressure was normal, but the protein content was 88 mg. per hundred cubic centimeters. At this time a more complete history was obtained, and it was learned that the patient really first became ill in July 1939, when he began to complain of nausea and stiffness of the neck.

The patient was discharged and was advised to return for follow-up examination. Two weeks later he was readmitted, with severe vertigo and loss of equilibrium on walking. Examination revealed progression of the bulbar signs, namely, atrophy and weakness of the right side of the tongue with fibrillations, paralysis of the entire soft palate and loss of the gag reflex, nasal regurgitation, choking on drinking water and pronounced nasal speech. The right eyelid was partially ptosed. The right pupil was 3 mm. and the left 4 mm. in diameter, and both pupils reacted promptly to light and in accommodation. The right cornea was analgesic. A fine, rapid nystagmus was present on looking to the left and a coarse, slower nystagmus on looking to the right. There was weakness of the right side of the body, except for the face, with generalized hyperreflexia, more pronounced on the right side than on the left, bilateral ankle clonus, loss of abdominal reflexes and bilateral Hoffmann and Babinski signs. Cerebellar signs were present bilaterally, but were much more pronounced on the right. There were some nuchal rigidity on attempting to flex the head and limitation of movement of the head in all directions. Atrophy of the intrinsic muscles of the right hand and the muscles of the right shoulder girdle was apparent; no fibrillations, however, were seen. Pain and temperature sensation was diminished in the distribution of the right trigeminal nerve; this was of the lamellar type and involved the medial portion of the face. There was also some loss of these modalities over the left side of the body below the eighth dorsal dermatomere. In view of the progressive character of the symptoms, a diagnosis of neoplasm in the region of the medulla was made.

The course of the illness continued downward. The patient was miserable on account of his dysphagia and had to be fed with a tube. Mucus accumulated in his throat, and he was unable either to expel or to swallow it. As a result he frequently became cyanotic, and it seemed that he would die within a short time. Examination of the fundi revealed the presence of a moderate degree of papilledema.

The foramen magnum was decompressed and the first cervical lamina removed. Dissection revealed a large tumor lying ventral to and compressing the pons, the medulla and the upper cervical portion of the cord, particularly on the right side. The mass was removed *in toto*, after which the vertebral arteries and the lower portion of the basilar artery were observed to lie flattened against the floor of the skull. Although the operation lasted nine and a half hours, the condition of the patient remained good, and he made a relatively uneventful recovery. Pathologic study of the tumor revealed it to be a neuroblastoma.

When seen one month later, on March 12, 1940, the patient stated that he was feeling well, except for slight weakness and numbness of the right side of the body, vertigo when he turned over quickly in bed and twitching of the right side of the face.

Arteriographic Visualization of Cerebrovascular Lesions. Dr. Sidney R. Govons, New York.

Cerebral angiography as a method of localizing intracranial lesions was first introduced by Egas Moniz in 1928. For the present, its use should be restricted to the localization of vascular lesions when air studies are likely to give little information or to misdirect therapy. The cerebrovascular lesions which can be visualized accurately are angiomas, aneurysms and occlusions of the internal carotid artery. The usefulness of the technic will depend to a large measure on the diagnostic acumen of the physician in the selection of suitable patients. No list of clinical indications for the use of this method will take the place of careful evaluation of the history and the physical findings.

However, several differential points are associated with these cerebrovascular lesions. Alternating syndromes involving the second, third, fifth and sixth cranial nerves with contralateral pyramidal signs are common. Transient seizures of varied types are frequent. In the cases presented, head bruits were not observed. Unilateral sensitivity of the carotid sinus may suggest the diagnosis. Increased intracranial pressure is absent: Puzzling neurologic pictures in cases in which air studies are not conclusive may at times be clarified by cerebral angiography. Finally, in cases of spontaneous subarachnoid hemorrhage the use of this new technic should be seriously considered.

The clinical data and the arteriograms in 5 cases of angioma, aneurysm or occlusion of the internal carotid artery are presented.

DISCUSSION

Dr. R. H. Groh, Washington, D. C.: My associates and I have been using arteriography for the past three and one-half years. I should like to make two comments in regard to the procedure. First, we prefer to inject the common carotid artery in order to obtain a picture of the circulation of the external as well as the internal carotid artery, since most of the meningeal blood supply comes from the former. We have encountered several cases of meningioma in which the angiographic picture was rather typical. The second point concerns the use of the technic with the aged. Egas Moniz reported a mortality of 2 per cent among persons with arteriosclerosis. We have been more fortunate, having had no difficulties at all in the advanced age groups. We made an arteriogram on a patient 78 years old.

The technic, we feel, is of definite value, and in many cases has led to a proper therapeutic attack, even when the encephalogram or the ventriculogram was not sufficiently revealing.

Dr. W. Freeman, Washington, D. C.: Arteriography has interested me greatly since Egas Moniz' original publication. At that time he used sodium iodide, and among his first patients there were convulsive seizures, hemiparesis and death. I prophesied then, erroneously, that the technic was too dangerous for application in this country. However, with the advent of thorium dioxide, the method became much more practicable, and I understand that there are now available in the chemist's laboratory, and also in the clinic, substances that do away with the theoretic objections to thorium dioxide. Personally, I have encountered none of the supposed difficulties from the use of this medium, and I believe it can be used with impunity.

When Dr. Gammon asked me to discuss Dr. Govons' paper, I was only too glad to do so, and I have brought along a slide and two arteriograms. The slide is a phlebogram of a small boy, on the basis of which I made a diagnosis of a cystic lesion with mural nodule, and this was verified at operation. The opera-

tive aftermath was unfortunate, as the patient died later, and the tumor proved to be a rather malignant oligodendroblastoma.

The arteriograms were taken on a patient who is still in the hospital. The diagnosis of traumatic arteriovenous aneurysm was obvious on looking at his eye. Three months after trauma the right eye protruded and had to be enucleated. Later the left eye became proptosed. An arteriogram of the left carotid artery showed that the thorium dioxide made a lake at the carotid siphon and went no farther. On the other hand, injection of the right carotid artery visualized a rather large aneurysm, with circulation in both cerebral hemispheres. Here, then, were symmetric aneurysms, the one on the right side being somewhat larger than the one on the left.

Since it was apparent from these arteriograms that the cerebral circulation was being carried on predominantly, or entirely, by the right carotid artery, it was thought advisable to compress this artery in order to force the left carotid artery to take over the circulation. When this was accomplished the right carotid artery was ligated, and soon afterward compression was begun on the left side. This was done until the patient could stand compression of the left carotid artery for thirty minutes. This artery also was tied off, but at the same time arteriograms were taken which revealed the alteration that occurred in cerebral circulation.

As can be seen here, this injection of an artery gave a wide circulation in the midline, with extension along both sides. There is evidently a large communication across the midline between the two carotid arteries. After the second, or left, carotid artery was ligated, the patient improved considerably. The proptosed eye receded. There is no longer any bruit, and, except for considerable dizziness, the patient is getting along satisfactorily. At no time, except during the early phases of compression, did he experience any disagreeable symptoms. At first he showed the carotid sinus phenomenon of which Dr. Govons spoke; that is, after pressure for ten seconds he went into syncope and convulsions.

I demonstrate these arteriograms as a means of bringing to the fore the usefulness of arteriography in studying the circulation and of demonstrating practical results in restoring to normal what looked like a hopeless condition.

DR. R. A. GROFF: I should like to ask both Dr. Freeman and Dr. Govons whether they use direct exposure or indirect injection of the artery.

DR. W. FREEMAN, Washington, D. C.: I use both. I prefer injection by needle when I can reach the artery. Sometimes in children that is difficult.

DR. S. GOVONS, New York: We always employ surgical exposure of the artery. We have tried inserting the needle directly into the carotid artery, usually without success. If the needle does enter, it may slip out because the injection has to be made rapidly if adequate records are to be obtained.

In our experience, the injection of thorium dioxide has been harmless. We have taken about forty arteriograms altogether. Several of the patients were elderly, of the age Dr. Groh mentioned, and none of them has experienced any ill effects from this procedure. Our only trouble is that the patients have some soreness of the throat for a day after the procedure; otherwise they have little discomfort.

I do not know whether thorium dioxide is carcinogenic. There is a great deal of discussion in the literature as to whether ill effects result from its radioactive powers, but in the amounts that we have used, and from a review of the literature, I feel that the method is perfectly safe. Elvidge (*A. Research Nerv. & Ment. Dis., Proc.* [1937] **18**:110-149, 1938) reviewed the literature on the toxicity of the substance. He has been using it and finds it apparently harmless.

As to the patient with the small berry aneurysm, the operation was successful in preventing the recurrence of subarachnoid hemorrhage. She apparently improved and went home; about three or four months later she was brought in unconscious, as an emergency. When I saw her that night, her neurologic picture was stationary and the spinal fluid was clear and normal. There was no evidence

that the central nervous system was involved. We fed her and gave her a blood transfusion, and after a day or two the stupor lessened and she was again discharged.

She returned three or four months later, again with sudden stupor, and at this time is was found that the blood sugar was low, about 40 mg. per hundred cubic centimeters. She had repeated attacks and finally died. Autopsy revealed the typical features of Simmonds' disease: The liver was about half its normal weight; both the adrenal glands weighed about 4 Gm., the normal being 20 Gm. The pituitary body was almost completely atrophied, although its structure could be seen microscopically. Why the patient had atrophy of the pituitary gland and such a severe pituitary syndrome I do not know.

Psychiatric Problems in Naval Practice. Dr. Luman H. Tenney and Dr. Dana L. Farnsworth, Philadelphia, Medical Corps, United States Navy.

The greatest problem confronting the navy psychiatrist is the constitutional psychopathic personality. Men of this type are entering the Navy in increasing numbers, despite the care taken to discover them at the time of enlistment. The number of cases surveyed from the naval hospital as psychopathic has increased from 32 to 54 per cent of the total number of psychiatric cases in the last six months. Failure to exclude men with such a disorder is due to the use of the cross section rather than the longitudinal method of study of the personality at the time of enlistment.

For the same reason, the diagnostic difficulty in differentiating the psychopathic from the psychoneurotic personality arises. Many conversion phenomena and many neurotic traits are found in the constitutional psychopathic personality. Short depressive states with suicidal attempts are common. If the cross section picture is used alone, the basic personality defects, uncovered only by a longitudinal study, are not noted and the diagnosis is usually wrong.

From the experience of one of us (L. H. T.) in an outpatient clinic of the Veterans Bureau, we state that this mistake was common after the last war. Many psychopathic conditions were wrongly diagnosed as psychoneurotic, with resultant confusion in treatment and cost to the taxpayer. The psychopathic person must not be treated for his emotional instability and inadequate performance by compensation, which only increases these defects.

An accurate history taken by trained social workers of the Red Cross and more alertness on the examiner's part with regard to adjustment to the home, school, work and society will give an adequate longitudinal section of the personality. Psychiatrists today do not have the excuse that was partially valid at the time of the last war, namely, that an unbiased personal history is unavailable.

Neuropsychiatric Problems in an Army General Hospital. Dr. Earl Saxe, Fort Dix, Medical Corps, United States Army.

This paper is a general survey of the problems which my associates and I have encountered in the neuropsychiatric section of an army general hospital. No attempt at a statistical analysis is made. The immensity of the neuropsychiatric problem in the last war is reviewed and a superficial comparison made with military experience to date. As in previous wars, the greatest percentage of our patients are psychoneurotic—a large number having conversion hysterias of the major sensorimotor type. Post-traumatic neuroses are frequent. Over 90 per cent of neurotic patients (including those with psychosomatic disturbances) are admitted to the medical, surgical, orthopedic, cardiac and gastrointestinal wards with a diagnosis of organic disturbance. As has been emphasized so frequently in military psychiatry, the importance of early recognition of the neuroses is obvious. By far the greater majority of our patients give evidence of their difficulty before entrance into the army. Their disorders are not caused by military service. Many patients with gastrointestinal and cardiac disorders have the common trait of dependence and emotional immaturity.

The neurologic problems are not unusual and include head injuries, diseases and injuries of peripheral nerves, multiple sclerosis, epilepsy and herniated intervertebral disk.

Psychiatric treatment is limited by the facilities and the time available. However, there is a surprisingly good response to superficial therapy by patients with a more acute condition and less involvement. Soldiering is a vocation that calls for a definite type of personality.

DISCUSSION ON PAPERS BY DRS. TENNEY AND FARNSWORTH AND DR. SAXE

DR. L. TWYEFFORT: I was extremely interested in the figures which Commander Tenney presented, and one's first impression is that they differ radically from the figures which one gets in a survey, say, of a cross section of persons with neuropsychiatric disorders in the general community. Certain factors may explain this. If one thinks in terms of the types of patients seen, for instance, in the consultation clinic of the Institute of the Pennsylvania Hospital, roughly 80 per cent are psychoneurotic and 20 per cent have a borderline psychosis. Of the 80 per cent, some 60 per cent suffer from a condition which comes under the general heading of anxiety state. Only occasionally over a period of at least three years has the diagnosis of "constitutional psychopathic inferiority" been made.

There may be some differences in the way various physicians use that term, and I wonder whether in the Army the term "constitutional psychopathic inferiority" does not apply to a type of personality disorder which one rarely sees in clinic practice in "average" communities, for the simple reason that the person with a personality which fits under that heading is one who rarely wants help. The "constitutional psychopathic inferiority" that I have read of in army reports sounds often like a mature picture of a "child behavior problem" or of "adolescent maladjustment." One sometimes makes that diagnosis in the case of a patient 16 or 17 years old. Such a person comes because he is forced to see the psychiatrist by the school authorities.

The nearest approach to constitutional psychopathic inferiority which we see at the institute is a condition which we tend to diagnose as "character neurosis." Persons with such a disorder have practically no somatic symptoms and come chiefly because of inability to adjust adequately to their social environment.

I was much interested in hearing Dr. Saxe's comments on the "psychosomatic disorders" and to hear how frequently that term is used in making a diagnosis. This seems to be in accord with the way in which more and more the residents and ward chiefs in a general hospital, such as the University Hospital, are willing to seek psychiatric evaluation of some of their cases of functional disorder, for the reason that they are becoming increasingly convinced that diagnoses of psychoneuroses can be made on a basis of positive evidence rather than on one of exclusion.

DR. L. H. SMITH: The point which I hoped Dr. Tenney would explain, and which he may comment on later, is the frequency of enuresis among men in the Navy. I made a study of surveys from the July 1941 to the January 1942 issue of the *United States Naval Medical Bulletin* and found increase during that time over the previous year.

As I recall, of 1,000 cases, 400 of them approximately were of psychiatric disturbances. At least 10 per cent, and I think a little more, were cases of enuresis. I wonder what kind of a neurosis was behind those cases, whether a psychopathic personality or a common type of behavior reaction that can be explained as peculiar to the service at the present time.

Dr. Saxe has given some figures elsewhere that parallel, I think, more or less exactly those of the naval service, except that the percentage of psychopathic personalities is higher in the Navy and the percentage of psychoneuroses is higher in the Army. That is, the two conditions are represented by a total of about 60 per cent of all the patients in the two services, the load being on the personality side in the Navy and on the psychoneurotic side in the Army. The two

groups, plus the epileptic patients (which numbered at least 10 per cent in the Army, and I think higher in the Navy), makes up about 70 per cent of all psychiatric casualties in the military service. Now, the Army has stated recently that there are only about 16 to 17 per cent of psychiatric casualties among draftees at the present time. Among the National Guardsmen and the volunteers they exceed 20 per cent. In other words, the last-mentioned groups have not had quite as close screening as the men who go through the examination centers.

Unfortunately, as every one knows, the draft situation has recently been changed, and the local board does not have the same power of rejection that it previously had. In other words, the screening is now thrown on the induction center, that is, on the examination center. Yet the authors have stated that 70 per cent of the men with whom they have trouble are those with obscure conditions which are not discernible in an objective examination. It looks as though the situation may become more serious. Those with experience in psychiatric and neurologic examination know that one cannot detect the psychoneurotic or the epileptic person if he does not tell the truth in the examination line, and the Selective Service Board at present has made it difficult to get the information of the longitudinal sort that gives one the opportunity of doing so.

DR. S. B. HADDEN: There is little doubt that the presently developed psychiatric observation of the men in the armed services is superior to that during the first world war. I was interested in hearing Dr. Saxe say that in an army general hospital there are certain types of cases which appear to be unique. Any one who has had experience with a large group of men performing a similar task will soon become aware that there are occupational disorders of organic and functional nature of which they had never before dreamed.

Psychoneurotic persons will constitute a grave problem in the armed services, as they do in civilian practice, and I should like to suggest that group psychotherapy be given further investigation and wider application. At the Presbyterian and the Philadelphia General Hospital my associates and I have been greatly impressed with the results obtained by the class treatment of psychoneurotic disorders. The results rival those secured even in time-consuming office procedures. Individual management in the army is impossible, but I believe group methods can be developed for application in the armed services.

DR. R. A. MATTHEWS: Dr. Tenney's comment on the difference between the percentage of psychopathic personalities seen in the active service and that at the Veterans Bureau was interesting. A possible explanation might be that the problem of the psychopathic personality is always, by necessity, an immediate one. The psychopathic person lives for the day only; hence his maladjustment is related to today's difficulties. When the immediate situation with which he is confronted changes, he may make a new, but temporary, adjustment to the community in which he finds himself. When he again has trouble, it arises on the basis of a new situation and is not the result of his connection with the service.

If, ten years from now, after he is out of the service, he finds himself failing to adjust to a job or offending against the social order, he will have some difficulty in relating the maladjustment to his military service. Hence fewer psychopathic offenders are seen by the medical officers in the veterans bureaus than by those in active service.

I should like to ask the speakers whether they see many acute schizophrenic-like psychoses which clear up quickly. The literature contains some references to psychoses which symptomatically appear to be malignant but the prognosis of which is better than would be expected in similar syndromes seen in civilian life.

Dr. Saxe mentioned the time of beginning treatment. This brings up the matter of where treatment should be instituted. A naval medical officer recently told me about an experience he had at sea. A sailor acquired what appeared to be a conversion hysteria, characterized by pain which radiated along the crest of the ilium and prevented locomotion. An attempt was made to treat this man

aboard ship by infiltrating the painful area with procaine. This resulted in his prompt relief. The man said that he felt fine and could walk without discomfort but an hour later he had to be restrained from jumping into the ocean in a suicidal attempt. This may be what Jelliffe would call a malignant conversion of a psychoneurosis by therapy applied at the wrong moment. The man still needed his conversion symptom as a means of solving his conflict.

DR. P. Q. ROCHE: The effect of compression of a large number of men into a disciplined organization is one which is common to both military and penitentiary life, and one may venture to say that to some extent the same basic anxieties are operative. In listening to Dr. Saxe's recital of his experiences with the neurotic and the psychotic expressions of military life, my attention was diverted at once to the similarity of such manifestations to those encountered in the penitentiary.

In the prison group this anxiety is manifest more frankly as a homosexual conflict, which finds more ready expression in the compressed prison life. May one conjecture whether homosexual conflict is also a basic factor in military breakdowns?

DR. EARL SAXE: In answer to Dr. Matthews' question concerning the acute psychoses, we have seen several interesting cases. One soldier, 29 years of age, came into the Army on January 5. By January 8 acute hallucinoses developed, and his auditory hallucinations were of a derogatory nature. He was hospitalized, and his condition completely cleared up in eight days, with good insight. Several weeks have elapsed, and he is getting along well.

In regard to early treatment, our experience thus far indicates the real value of active, intensive treatment. I had a patient with paralysis of one arm. By means of narcosis induced with sodium amytal and suggestion, he regained power in that arm. While he had his paralysis, he was very happy, pleasant and seemingly well adjusted. When his extremity improved, anxiety, headaches and insomnia developed. It is questionable whether such partial treatment is desirable.

We have had only one attempt at suicide in our service, and we have been active now about nine months. I neglected to mention that we see in our service 33 per cent of all the patients admitted to this general hospital.

In answer to Dr. Roche's question about homosexuality, we are not familiar enough with our patients to know just how important a factor that is. I believe the statistics of this war will be different from those of the last, chiefly because our criteria of diagnosis are different.

Book Reviews

Psychotherapy with Children. By Frederick H. Allen. Price, $3.50. Pp. 311. New York: W. W. Norton & Company, Inc., 1942.

The experience of seventeen years in the Philadelphia Child Guidance Clinic serves as the basis of the material which Dr. Allen describes in this remarkable book. The opening chapters deal with the underlying conceptions on which therapy rests. These are necessarily incomplete, as knowledge of normal development is still incomplete. The rest of the book is devoted to the consideration of carefully selected details which serve to illustrate the basis for the generalizations. The reader is not distracted by controversy, pretensions to originality or claims to statistical success and is thus freed to focus his attention completely on the subject at hand.

The unique feature of Dr. Allen's method is its predominant emphasis on the physician-child relationship. The content of the child's communication is not to be interpreted as having significance on its own account, but is to be regarded only as a symbolic statement of the child's relationship to the therapeutist or the child's struggles with that relationship. These arise in connection with the child's attitude toward himself. By assisting the child to realize that only he can help himself and by recognizing the child's dignity and uniqueness, the physician performs his task without the necessity of searching for origins or of concerning himself with the specific symptoms which brought the child to the clinic. There, therefore, is an absence of the usual classifications of disorders. Symptoms are unimportant except as they reveal a particular reaction to the therapeutist.

The period of treatment is thus apparently reduced to a minimum, in spite of the fact that the so-called transference cure is carefully avoided. Such a method is often quicker, but is deprecated as dependent on the seduction of the patient by the therapeutist. Nor is this procedure comparable with what is known as "the analysis of the transference," although there are certain similarities. Dr. Allen believes that the child does indeed project on the physician, but this does not lead Dr. Allen to search the origins of these projections or to regard them as fixed. To him they reveal the child's attempts to find himself as an entity in a relationship with an adult. If the therapeutist is a mature adult, the child will be enabled to find his proper place as a child. This the child is ceaselessly struggling to do, at the time without success because of some lack or distortion in the family situation. It is the ebb and flow of this struggle which the doctor must perceive through whatever material is presented in conversation, play or behavior.

Nothing short of inspired is the requirement that the mother or guardian shall have a simultaneous appointment with a social worker. This plan tacitly acknowledges the fact that the family shares the responsibility for the difficulties. Any overt attempt to assign responsibility by the physician or the social worker is entirely extraneous, however. The mother is given some insight into the role best assumed by her to assist to the maximum the child's efforts to alter his present behavior.

Because so much is eliminated in this procedure, one might receive the impression of oversimplification by a single track mind. This is far from the case. There is a clear recognition of complexity illustrated in the subtle appreciation of the symbolic nature of the child's remarks, in the sensitiveness to the delicate balances present in the processes of growth and change and in the astute perception of positive values exactly in those symptoms which often present themselves as aggressive and destructive. The book might be read profitably for enlightenment on this last point alone, if for no other.